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THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

I. STUDIES OF NORMAL SUBJECTS AND OF THOSE WITH OCCLUSIVE ARTERIAL DISEASE AND HYPERTHYROIDISM*

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KOCH,[1] in 1922, was the first investigator to determine the speed of circulation in man. He injected a solution of potassium ferrocyanide into the cubital vein of one arm and collected samples of blood from the cubital vein of the other arm at five-second intervals. He found that the average time required for the blood to traverse such a circuit was twenty-two seconds, with a range of twelve to twenty-seven seconds in different individuals. Since that time, numerous other methods have been introduced for estimating the velocity of the blood flow. An active radium deposit has been injected into a vein at the elbow and its arrival at the opposite brachial artery detected by means of a counting chamber.[2] Calcium chloride,[3-6] calcium bromide,[7] calcium gluconate,[8, 9] endoiodine,[10] and magnesium sulfate[11, 12] have been injected intravenously, and the interval elapsing between the injection of the solution and the occurrence of a warm sensation in the throat has been considered the circulation time between the arm and the tongue. Dehydrocholic acid (decholin[13-22]), which causes a bitter taste in the mouth, and saccharin,[23-31] which causes a sweet taste in the mouth, have also been utilized for determining the speed of blood flow between these same two points. Various dyes have been injected intravenously and the speed of blood flow determined by analyzing samples of blood collected from the carotid, femoral, and radial arteries.[32-36] Histamine has been utilized to determine the circulation time between a vein of the arm or foot and the capillaries of the face.[37-39] Sodium cyanide, which causes a sudden

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deep inspiration after its intravenous injection, has been used to estimate the circulation time[40-47] from the arm to the carotid sinus. Ether and paraldehyde have been employed to measure the pulmonary circulation time.[48-51]

These methods have, for the most part, dealt almost entirely with the velocity of the blood flow in the peripheral venous and pulmonary systems. Exceptions are to be found in the works of Hamilton, Moore, Kinsman, and Spurling,[32-35] of Blumgart and Yens,[52] of Klein and Heinemann,[33] and of Robb and Weiss,[45] whose investigations included speed of flow of blood in peripheral arteries, as well. No attempts were made to estimate the speed of flow of blood in the arteries alone, although Blumgart and Weiss did assume that 3.3 seconds are required for the blood to flow from the left ventricle to the brachial artery.

In 1929, Kahler,[5] by timing the occurrence of the warm sensation in the tongue, perineum, hands, and feet after the intravenous injection of calcium chloride, measured for the first time the velocity of the flow of blood in a combined venous-arterial circuit. Leschke[6] and Katz[7] confirmed Kahler's work. In 1936, Spier, Wright, and Saylor[53] utilized the same principle by means of a solution containing magnesium sulfate, calcium gluconate, and sodium chloride.

Thus, it is apparent that methods for determining the speed of flow of blood in the arteries of man are lacking. It has, therefore, been the purpose of this investigation to determine, if possible, the speed of the flow of blood in both the arteries and the veins of a group of individuals considered to have normal circulation, and in groups suffering from occlusive arterial disease and hyperthyroidism.

THE SOLUTION AND METHOD OF STUDY

Constituents of the Solution and Its Mode of Action.—The solution we have used is that described by Spier, Wright, and Saylor.[53*] It contains 42 gm. of magnesium sulfate, 16 gm. of calcium gluconate, 0.9 gm. of sodium chloride, and 1.0 mg. of copper sulfate in each 100 c.c. of distilled water. The reasons for using a solution containing these ingredients have been discussed by Spier, Wright, and Saylor. The magnesium sulfate is used because of the subjective sensation of warmth that it produces, and the calcium gluconate and sodium chloride are added to minimize any possible toxic effects of the magnesium salt. Copper sulfate is added to the solution solely as a preservative. When this solution is injected intravenously, it produces a sensation of warmth or heat throughout the body, but particularly, and usually very distinctly and unmistakably, in the throat, perineum, hands, and feet. The exact mechanism involved in the production of this burning sensation is not known.

Description of the Method.—Before the test is performed, the subject is carefully instructed what to expect. He is told that something is to be injected into his vein, that it will produce a sensation of warmth throughout his body in less than a minute, but that separate from this general feeling of body warmth he will feel distinctly a flash of heat in his throat, perineum (crotch), hands, and feet. In some instances the subject feels only the flash of heat in the sites mentioned.

*The solution was made available through the courtesy of Merck and Co., Rahway, N. J.

He is requested not to become confused, but to pay close attention, for, although the sensation is not exactly pleasant, it is certainly not unpleasant. He is instructed to report immediately the site of the sensation by saying sharply, "tongue," "crotch," "hands," or "feet." In a subject with a normal circulation the sensation that occurs in the hands usually appears simultaneously in both. This likewise holds true for the feet. The subject is told this, but it is also made clear that the sensation may occur in one hand before it occurs in the other, or in one foot before it occurs in the other. Under these circumstances he should say, for example, "right foot," or "left foot."

Two cubic centimeters of the solution described previously are drawn into a 3 c.c. syringe which has been fitted with a 20-gauge needle. With the patient at rest and the arm at the level of the heart, the needle is inserted into a vein overlying the antecubital fossa. After the tourniquet has been released, a pause of three to five seconds is made before the solution is injected. This is done to allow the circulation to return to its original state in case it has been disrupted by the tourniquet or by any mechanical manipulation of the needle. Then the solution is injected as rapidly as possible. When the injection is started, the demonstrator, or person performing the test, says the word, "go," and a helper starts the stop watch. The stop watch is then transferred to the demonstrator, and as the subject calls out the various sites where the sensation occurs, the time is taken and duly recorded by the helper. By this means, that is, with the aid of another person, we have been able to get more accurate results than if the test were performed by one person alone.

Occasionally, especially if the patient is the least bit unstable, the first test will be unsatisfactory because of the rapidity with which reactions occur, and because, despite explicit and careful instructions, the exact description of the sensation cannot be fully explained. This result, fortunately, is infrequent, and a second test, done within five or ten minutes, may prove to be perfectly satisfactory. In the usual case, however, only one test is necessary.

Definition of Terms.—What has been determined in all these studies is the time elapsing between the beginning of the injection into a vein and the occurrence of the sensation of warmth in the throat, hands, perineum, and feet, respectively. We wish to emphasize that we do not know that the sensation of warmth in the hands, for example, indicates that the solution injected has just arrived at the hands, but for the purpose of simplification we have assumed that this reasoning is correct. Thus the expressions "arm to tongue," "arm to hand," "arm to perineum," and "arm to foot" indicate the time elapsing between injection of the solution into a vein at the elbow and the occurrence of the sensation in the tongue, hands, perineum, and feet, respectively. Whenever patients failed to perceive the sensation of warmth, the designation "blank" has been used. Such periods of time as those indicated include the time required for the solution injected to pass through the arm vein, the superior vena cava, the right side of the heart, the pulmonary circulation, the left side of the heart and, finally, the peripheral arteries.

In this study we have been interested primarily in the speed of blood flow in peripheral arteries, but the test does not give any direct indication of this, for there is no way of knowing when the injected solution leaves the left ventricle. However, this can be estimated with reasonable accuracy. It seems reasonable to assume that by the time the solu-

tion reaches the tongue, it will have traversed a distance down the aorta equal to that between the left ventricle and the tongue. The time required for the blood to flow this distance appears to be about one second, although we cannot say that this is an established fact, and neither can we find any direct proof of this. Hamilton, Moore, Kinsman, and Spurling[32] have considered that one second is required for blood to travel from the jugular vein to the heart. Since the total cross-sectional area of the great veins emptying into the right side of the heart is about twice that of the root of the aorta, and since the velocity of flow is inversely proportional to the cross-sectional area, the time required for the blood to flow from the left ventricle to the tongue appears to be even less than one second.

Because an unknown factor would be added in calculation of the time required for blood to traverse peripheral arteries, we have not included the assumed and reasonably correct time of one second required for blood to flow from the left ventricle to the tongue in our calculations. If we had done so, the "arm-to-foot time," minus "arm-to-tongue time," plus one second, would give a figure indicating the time elapsing during the passage of the solution from the left ventricle to the feet. Since the time required for blood to traverse the distance from the left ventricle to the tongue is relatively constant, we have considered that it may be included in calculations for comparative purposes. Therefore, the "left-ventricle-to-perineum" time, or "ventricle-to-perineum" time, has been calculated by subtracting the "arm-to-tongue" time from the "arm-to-perineum" time. Similarly, "arm-to-hand" time, minus "arm-to-tongue" time, equals "ventricle-to-hand" time, and "arm-to-foot" time, minus "arm-to-tongue" time, equals "ventricle-to-foot" time. It is interesting to note that G. N. Stewart,[54] in 1894, used this same principle to demonstrate the rate of blood flow from the root of the aorta to the crural artery in the rabbit.

We emphasize again that the periods of time so designated are not actual, but subject to the qualifications noted in the foregoing. By this method we have made an attempt to evaluate the speed of flow of blood throughout the arterial system—from the left ventricle to the hands, perineum, and feet. We are fully aware that the figures so obtained are not absolutely accurate, and that the designation "ventricle-to-hand" time, for example, is not an entirely true one, but we do feel that for the first time an attempt has been made to demonstrate the velocity of the flow of blood in the arteries of man.

Value of the Method.—There are certain qualifications which are essential to a good method of injecting any substance intravenously for circulation-time studies. These are enumerated below, and it is our opinion that the method we have been using fulfills these requirements.

1. *The substance must be nontoxic in the amounts utilized.* Neuwirth and Wallace[55, 56, 57] have shown that the narcosis obtained from mag-

nesium salts is dependent upon the dosage and absorption of magnesium and the concentration of magnesium in the serum. They concluded that symptoms of depression in the dog appear only when the serum magnesium content reaches 5 mg. per 100 c.c., and that this also holds true for man. They stated that 0.25 gm. of magnesium sulfate per kilogram of body weight is the minimal effective dose in man, and that such a dose will raise the serum magnesium to 5.6 mg. per 100 c.c.

Since the amount of magnesium contained in the solution we have been using is but 0.84 gm. per 2 c.c., a normal person weighing 70 kg. would be receiving but 0.012 gm. of magnesium per kilogram of body weight, a safe working margin, and far below the dose, even if repeated many times in one day, required to produce slight depression. The amount of calcium injected is small and, we believe, should occasion no concern.

2. *The substance should be eliminated from the system quickly and easily, so that repeated tests may be performed without jeopardizing the welfare of the patient.* Mendel and Benedict,[58, 59] in their work on the paths of excretion of inorganic compounds, showed that there is only a small excretion of magnesium sulfate into the intestines following subcutaneous injection into animals, and that the kidneys are predominantly important in the elimination of the excess magnesium sulfate. Furthermore, this excretion takes place within forty-eight hours, chiefly during the first twenty-four hours. They showed also that the increased excretion of magnesium by the kidneys is accompanied by a marked rise in the urinary output of calcium. It seems established, therefore, that the principal components of the solution we have injected are excreted from the body probably within twenty-four hours, chiefly by way of the kidneys.

3. *The substance should have no effect upon the pathologic condition being studied.* In our studies, we have perceived nothing to indicate that the injected solution influenced the various diseases that some of the patients had.

4. *The procedure should in itself be simple, and when the end point is subjective it should be comprehended easily by the person on whom the test is done.* This is true for the test that we have used except under circumstances that will be mentioned later.

Fallacies of the Method.—Objection may be offered to any method, such as the one we have described, which depends for accuracy on the patient's cooperation and ability to signal the sensation. Moreover, the exact mechanism by which the sensation is produced is still undetermined. It is not known whether the sensory nerves are stimulated at the instant the blood bearing the solution reaches the hand, for example, or whether the stimulation occurs some time later. Certainly the solution must stimulate sensory nerve endings either in the walls of the vessels or in the perivascular tissues. Whatever the mechanism, some time must be required for stimulation of the sensory nerves and perception of the

sensation. Although we believe that this "reaction time" is short, the method may be criticized because we do not know exactly what the reaction time is. To support the accuracy of the method one would need to prove that the reaction time is negligible, which we cannot do. If the reaction time were known to be constant under the conditions of our study, comparative values for speed of circulation could be determined. Unfortunately, we do not know that the reaction time is constant.

Hewlett,[60] Hewlett and Van Zwaluwenburg,[61] Freeman,[62] and Prinzmetal and Wilson,[63] by the use of the plethysmograph, and Stewart,[64] Taylor,[65, 66] and Pickering,[67] by means of the calorimeter, have made valuable observations upon the volume, not velocity, of peripheral blood flow. We feel that the disadvantages of the test used by us, namely, that it is subjective, and that the "reaction time" is unknown, are outweighed by the advantages, in that it allows us to calculate blood flow from the heart to the periphery in terms of speed.

Reactions.—In this entire study, 634 injections were made into 217 patients. The safety of the method was demonstrated by the fact that the reactions which occurred were very few and mild. In several instances in which a small amount of the solution infiltrated the perivascular tissues, considerable pain and a severe burning sensation, lasting for several hours, resulted, but there was no subsequent sloughing or necrosis. Venous thrombosis occurred in only two instances. We anticipated no trouble from extravascular injection, for earlier we had injected the solution into the extravascular tissues of rabbits' ears without producing reactions other than edema.

RESULTS OF STUDY

Normal Subjects.—One hundred sixty-five tests were performed on sixty normal subjects. A large number of these tests were carried out under "basal conditions," a term signifying that the subject had been at complete rest for at least half an hour, without food for at least eighteen hours, and was in a room the temperature of which was kept constant. These conditions did not obtain in the group of patients who were studied under "uncontrolled conditions."

1. *Under Controlled Conditions.*—The results shown in Table I give the frequency distribution and mean of seventy-three tests performed on thirteen subjects. The range of the "arm-to-tongue" time is not great, and the average, 13.7 seconds, although one second more rapid than that reported by Spier, Wright, and Saylor,[53] is nevertheless in close agreement with all other circulation time tests that depend upon a reaction in the tongue or throat.

The range of the times for "arm to hands," "arm to perineum," and "arm to feet" was considerably greater, especially so in the case of the "arm-to-feet" times. In general, those with the longer "arm-to-tongue"

times had longer "arm-to-feet" times. In a few instances, but seven to nine seconds elapsed from the time the sensation was perceived in the tongue until it was perceived in the feet. In other instances as much as forty-three seconds elapsed. That such a variability was possible in different individuals was at first something of a surprise, but as more and more tests were done it was soon noted that such variations were by no means rare. In fact, the literature on the time required for circulation over shorter distances than from arm to feet indicates that there is a wide variation in speed of blood flow in different individuals.

TABLE I

NORMAL SUBJECTS UNDER CONTROLLED CONDITIONS
(SEVENTY-THREE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	3	0	0	0	0	0
10-14	47	4	2	0	0	0
15-19	21	29	16	19	2	2
20-24	2	20	29	27	7	8
25-29	0	12	11	13	12	9
30-34	0	7	13	12	7	11
35-39	0	0	1	2	15	13
40-44	0	0	0	0	6	6
45-49	0	0	0	0	4	4
50-54	0	0	0	0	5	4
55-59	0	0	0	0	1	1
Blanks	0	1	1	0	14	15
Mean*	13.76±.20	21.22±.41	23.68±.43	23.60±.48	34.28±.85	34.0±.85
Stan. dev.*	2.65	5.14	5.41	6.08	9.73	9.57

*Time in seconds.

In the same individual, however, if the test can be done under conditions as nearly the same as possible from day to day, little variation is noted (Table II). In Case 1, the test was done at the same hour on the days as noted. The patient had had no breakfast and had rested for at least an hour. In Case 2, the test was done at different hours of the day and, although no heed was paid to whether or not the patient had eaten, he had been at complete rest for more than an hour. If the values for the skin temperature are charted on the ordinates, and the values for the "arm-to-hand" or "arm-to-foot" times are charted on the abscissae, there is shown to be a rough correlation between circulation time and skin temperature.

Studies of the time required for the blood to flow from the left ventricle to the designated sites are shown in Table III. In this series of cases, an average of 7.6 seconds was required for the blood to flow from the left ventricle to the perineum. The values fell largely between five and nine seconds. An average time of 9.8 seconds was required for the blood to flow from the left ventricle to the hand, and the variation was

TABLE II

CIRCULATION TIMES IN SAME INDIVIDUAL UNDER BASAL CONDITIONS

CASE	DATE (1937)	BLOOD PRESSURE, MM. OF MERCURY	PULSE RATE	ROOM TEMP., DEGREES C.	SKIN TEMPERATURE (DEGREES C.)				ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
					R^1 TOE	L^1 TOE	R^3 FINGER	L^3 FINGER	TIME IN SECONDS					
1	8-23	102/68	88	25.3	28.5	29.0	33.2	32.3	14	24	24	22	36	35
	8-24	94/58	80	25.5	29.8	29.8	33.3	32.4	14	22	24	23	37	35
	8-26	92/70	68	25.3	28.8	29.4	--	--	15	24	22	23	39	39
	8-27	104/64	76	25.3	26.6	28.3	31.3	31.6	15	23	25	25	41	41
	8-30	106/64	72	25.3	32.0	33.1	35.3	35.3	14	22	24	24	36	35
	8-31	104/64	72	25.6	31.5	32.2	36.0	36.0	13	23	22	21	33	33
	9- 1	102/68	76	25.0	28.1	28.4	35.3	32.1	15	25	24	22	37	38
	9- 2	96/58	76	25.0	30.5	31.5	33.5	33.5	14	22	23	21	35	35
	9- 3	92/68	72	25.2	31.5	31.9	34.4	34.9	13	20	19	21	32	33
2	7-13	124/66	72	25.2	24.9	25.6	32.8	33.2	9	14	16	16	21	21
	7-13	120/68	76	25.2	25.8	26.5	33.4	33.3	11	16	15	15	20	20
	7-14	114/72	76	25.2	31.8	32.3	33.8	33.2	11	16	18	15	21	21
	7-14	106/76	68	25.0	30.8	31.5	33.2	32.7	10	17	19	17	25	24
	7-15	104/62	64	25.0	27.8	27.8	32.1	32.5	11	16	20	19	23	23
	7-15	112/60	68	24.8	26.0	26.0	28.5	28.5	12	18	22	22	28	28
	7-19	112/60	64	25.0	27.4	28.3	31.5	31.5	13	18	21	22	26	26
	7-19	120/60	80	25.0	25.9	26.6	31.3	31.1	11	18	21	21	27	27

even greater, that is, five to fourteen seconds. This greater variation was expected, for studies have shown that whereas a number of factors influence circulation in the hand, they probably influence circulation to the perineum very little. The "ventricle-to-feet" times cover a rather wide range, with the greatest number of values occurring between fifteen and twenty-four seconds, and with a mean of 20.6 and 20.3 seconds for the right and left foot, respectively. These calculations of "ventricle-to-hand," "ventricle-to-perineum," and "ventricle-to-foot" times are the first attempts to determine speed of arterial circulation in man, with the exception of the study of Blumgart and Weiss,[68] who estimated that 3.3 seconds are required for blood to flow from the left ventricle to the brachial artery.

TABLE III

NORMAL SUBJECTS UNDER CONTROLLED CONDITIONS
(SEVENTY-THREE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	6	5	4	0	0
5-9	51	29	32	3	3
10-14	14	34	32	7	8
15-19	1	4	4	18	16
20-24	0	0	1	16	16
25-29	0	0	0	8	10
30-34	0	0	0	4	3
35-39	0	0	0	3	2
Blanks	1	1	0	14	15
Mean*	7.61	9.88	9.78	20.61	20.32

*Time in seconds.

2. *Under Uncontrolled Conditions.*—The subjects included hospital patients, usually at rest in bed, and workers and assistants about the laboratory. The tests were done after short periods of rest.

One hundred two tests were performed on fifty-one subjects (Table IV). The results agree favorably with those obtained when the patient was under controlled conditions, except that in this group the average "arm-to-foot" time was two seconds less. We have no explanation for this fact unless it be that most of these tests were done during the warm summer months, when the subject's surface temperature was influenced by the environmental temperature, which was greater than that of the constant-temperature room. As will be shown in a subsequent publication, environment exerts a great influence upon the circulation time to the extremities. The skin temperatures of patients who were at rest in a constant-temperature room at 25° C. were, as a rule, considerably lower than those of patients who were not at rest in a constant-temperature room. In the former group, the circulation times were consequently increased. Further analysis reveals that in the "controlled group" no sensations were perceived in the right and left foot in fourteen and fifteen instances in seventy-three tests, while in the "uncontrolled

group'' the respective figures were twelve and thirteen, respectively, in one hundred two tests. The proportionate increase in ''blanks''* in the ''controlled group,'' as contrasted to the number that occurred in the ''uncontrolled group,'' may have been due to the lower environmental temperatures at which the studies in the former were carried out. If the mean figures for the ''arm-to-foot'' times in the ''controlled'' and ''uncontrolled'' series of studies are dealt with statistically, no significant difference is found, for 34.28 minus 32.17, or 2.11 seconds, is less than three times the square root of the sum of the squares of the two probable errors, or 1.09.

TABLE IV

NORMAL SUBJECTS UNDER UNCONTROLLED CONDITIONS
(ONE HUNDRED TWO TESTS ON FIFTY-ONE SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	5	0	0	0	0	0
10-14	65	6	4	2	0	0
15-19	25	47	24	28	0	0
20-24	6	25	35	36	20	18
25-29	1	15	18	14	28	29
30-34	0	4	13	14	13	15
35-39	0	1	5	4	7	6
40-44	0	2	1	2	7	7
45-49	0	0	0	0	10	10
50-54	0	0	0	0	3	2
55-59	0	0	0	0	1	1
60-64	0	0	0	0	0	0
65-69	0	0	0	0	1	1
Blanks	0	2	2	2	12	13
Mean*	13.68±.24	20.99±.37	23.47±.40	23.47±.41	32.17±.69	32.02±.68
Stan. dev.*	3.52	5.52	6.00	6.09	9.72	9.46

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	12	11	10	0	0
5-9	73	36	41	3	3
10-14	11	43	36	30	29
15-19	4	10	13	26	27
20-24	0	0	0	10	10
25-29	0	0	0	13	13
30-34	0	0	0	5	4
35-39	0	0	0	2	2
40-44	0	0	0	1	1
Blanks	2	2	2	12	13
Mean*	7.28	9.80	9.80	18.67	18.48

*Time in seconds.

The results of our study of these two groups of normal subjects lead us to believe, therefore, that when circulation-time tests are to be done on a group of individuals, it matters little whether these individuals are

*As stated in "Description of Terms," the term "blank" is used to designate failure of the patient to perceive the sensation of warmth.

under absolutely basal conditions or not, for the mean of the results under basal and nonbasal conditions will be insignificantly different. Obviously, in study of patients not under basal conditions, they should be given the opportunity to recover from any undue physical effort and excitement and kept as quiet as possible under the circumstances. And, naturally, if one is to compare results of repeated studies of one patient, the circumstances of the study should be as nearly identical as possible each time.

Thromboangiitis Obliterans.—In Table V are presented the results of twenty-three tests on fifteen patients suffering from thromboangiitis obliterans. These tests were carried out, as a rule, under basal conditions, although in a few instances the patient had recently had food. Analysis of these cases reveals that the "arm-to-tongue" time is very

TABLE V

THROMBOANGIITIS OBLITERANS

(TWENTY-THREE TESTS ON FIFTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	10	1	0	0	0	0
15-19	13	9	5	6	0	0
20-24	0	6	8	5	2	2
25-29	0	4	8	5	3	2
30-34	0	2	1	4	2	2
35-39	0	1	1	3	2	0
40-44	0	0	0	0	0	0
45-49	0	0	0	0	1	2
50-54	0	0	0	0	2	2
55-59	0	0	0	0	1	1
60-64	0	0	0	0	0	0
65-69	0	0	0	0	0	0
70-74	0	0	0	0	0	1
Blanks	0	0	0	0	10	11
Mean*	14.48±.40	22.35±.87	23.74±.75	25.30±1.00	36.08±2.23	40.58±2.98
Stan. dev.*	2.86	6.22	5.30	7.13	11.92	15.33

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	5	1	2	0	0
5-9	14	12	7	0	0
10-14	2	9	9	3	2
15-19	2	1	3	4	4
20-24	0	0	2	2	0
25-29	0	0	0	0	1
30-34	0	0	0	2	2
35-39	0	0	0	2	2
40-44	0	0	0	0	1
45-49	0	0	0	0	0
50-54	0	0	0	0	0
Blanks	0	0	0	10	11
Mean*	7.30	9.13	10.83	22.77	25.00

*Time in seconds.

slightly longer than that of normal subjects (Tables I and IV). Whether this finding is significant in a small group of cases is difficult to say. Spier, Wright, and Saylor[53] obtained similar results.

The average "arm-to-foot" time is increased slightly in thromboangiitis obliterans (Tables I, IV and V), and the range is greater. The number of "blanks" occurring in the feet in thromboangiitis obliterans comprises 45 to 50 per cent of the total number of tests, as compared with 19.2 per cent in the normal subjects. Since the perception of the sensation in the feet depends in large part on the warmth of the skin, and since the extremities in thromboangiitis obliterans are, on the whole, relatively cold, the explanation of this occurrence becomes immediately evident.

The average "arm-to-foot" time in thromboangiitis obliterans, 36.1 and 40.6 seconds, respectively (Table V), is less important than the results in individual cases, for the extent of the disease varied widely in different cases. We have observed that clinical evidence of marked impairment of arterial circulation is not necessarily associated with a prolonged "arm-to-foot" circulation time. However, it may be stated as a generalization that usually the circulation time is more prolonged in cases of severe ischemia than in cases of milder ischemia.

Our conclusions regarding use of this solution for diagnosis of, and prognosis in, thromboangiitis obliterans are that it has no value. The circulation time depends upon too many factors, such as the vasomotor control of the extremities. A normal person, for instance, may have no disease of his arteries, yet his extremities may be cold and the circulation time to his extremities may be prolonged, or no sensation at all may result.

The effect of fever induced artificially by intravenous injection of typhoid vaccine on the speed of blood flow is shown in Table VI. As

TABLE VI

EFFECT OF FEVER INDUCED BY INTRAVENOUSLY INJECTED TYPHOID VACCINE ON CIRCULATION TIME IN THROMBOANGIITIS OBLITERANS

CASE		ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
		TIME IN SECONDS					
1	Before fever	11	16	21	21	Blank	Blank
	During fever	11	15	18	18	Blank	26
2	Before fever	16	22	25	26	Blank	Blank
	During fever	14	20	21	17	26	35
3	Before fever	18	21	28	28	Blank	Blank
	During fever	16	23	27	27	38	46
4	Before fever	19	33	24	37	57	57
	During fever	17	32	29	28	42	42
5	Before fever	15	23	29	36	46	Blank
	During fever	12	19	17	17	25	32
6	Before fever	12	19	21	16	26	28
	During fever	11	15	13	14	18	18
7	Before fever	16	26	29	30	37	70
	During fever	16	27	30	30	39	40

expected, the results were not uniform, for the degree of vasodilatation induced by fever is not uniform in all extremities in thromboangiitis obliterans. Usually, however, fever increased the speed of circulation.

Arteriosclerosis Obliterans.—What has already been written in regard to speed of circulation in thromboangiitis obliterans applies in cases of arteriosclerosis obliterans, as well. The results of the studies are shown in Table VII. The average figures for "arm-to-tongue," "arm-to-hand," "arm-to-perineum," and "arm-to-foot" times are all prolonged when compared with the figures obtained in a study of normal subjects (Table IV). Perhaps this indicates a general slowing of circulation in individuals of advanced age with arteriosclerosis. The percentage of "blanks" in the feet was 52 and 41 per cent in the right and left foot, respectively.

TABLE VII

ARTERIOSCLEROSIS OBLITERANS

(TWENTY-SEVEN TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	6	0	0	0	0	0
15-19	12	4	4	3	0	0
20-24	4	9	5	6	0	1
25-29	3	1	6	5	3	3
30-34	1	3	4	5	3	2
35-39	1	2	1	2	1	1
40-44	0	3	3	2	3	4
45-49	0	1	1	0	0	1
50-54	0	2	1	2	1	0
55-59	0	0	0	0	0	0
60-64	0	0	0	0	2	1
65-69	0	0	0	0	0	1
70-74	0	0	0	0	0	2
Blanks	0	2	2	2	14	11
Mean*	18.48±.77	29.8±1.56	29.16±1.31	29.80±1.31	40.15±2.29	44.06±2.86
Stan. dev.*	5.93	11.53	9.68	9.68	12.25	16.97

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	5	3	2	0	0
5-9	8	8	7	0	1
10-14	6	7	8	1	2
15-19	3	6	7	5	3
20-24	1	1	1	2	1
25-29	2	0	0	3	4
30-34	0	0	0	1	2
35-39	0	0	0	1	1
40-44	0	0	0	0	0
45-49	0	0	0	0	1
50-54	0	0	0	0	0
55-59	0	0	0	0	1
Blanks	2	2	2	14	11
Mean*	10.68	10.96	11.28	22.38	26.06

*Time in seconds.

It is to be expected that in these cases the circulation times will be prolonged, and that the percentage of "blanks" in the feet will be relatively large. However, in one case of rather marked sclerosis of the peripheral vessels in which both dorsalis pedis and posterior tibial arteries were occluded, the circulation time to the feet on two tests was on the fast side of normal. And in another case, in which occlusion of the popliteal artery had occurred six weeks previous to study, with obvious evidence of vascular insufficiency, repeated tests showed a more rapid circulation in the more affected leg than in the other. These experiences lead us to question the value of the test in cases of arteriosclerosis obliterans.

Hyperthyroidism.—It is known that in cases of hyperthyroidism the velocity of the peripheral venous blood flow is increased. Tables VIII and IX indicate that the speed of arterial circulation is also increased.

TABLE VIII

EXOPHTHALMIC GOITER AND ADENOMATOUS GOITER WITH HYPERTHYROIDISM (THIRTY-ONE TESTS ON FOURTEEN PATIENTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	9	0	0	0	0	0
10-14	22	14	9	7	1	1
15-19	0	17	16	19	10	10
20-24	0	0	5	5	6	6
25-29	0	0	0	0	7	7
30-34	0	0	0	0	0	1
Blanks	0	0	1	0	7	6
Mean*	10.39±.29	14.93±.34	16.23±.39	16.64±.35	21.29±.54	21.76±.64
Stan. dev.*	2.42	2.79	3.14	2.87	3.95	4.73

*Time in seconds.

TABLE IX

EXOPHTHALMIC GOITER AND ADENOMATOUS GOITER WITH HYPERTHYROIDISM (THIRTY-ONE TESTS ON FOURTEEN PATIENTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRIC TO R. FOOT	VENTRICLE TO L. FOOT
0-4	15	8	6	1	1
5-9	16	22	25	9	9
10-14	0	0	0	12	12
15-19	0	0	0	2	2
20-24	0	0	0	0	0
25-29	0	0	0	0	1
Blanks	0	1	0	7	6
Mean*	4.58	5.76	6.25	10.58	11.28

*Time in seconds.

In exophthalmic goiter and adenomatous goiter with hyperthyroidism the average "ventricle-to-perineum" time is 4.6 seconds, the average "ventricle-to-hand" time is about six seconds, and the average "ven-

tricle-to-foot'' time is about eleven seconds. In normal subjects under uncontrolled conditions (Table IV), the average ''ventricle-to-perineum'' time is 7.3 seconds, the average ''ventricle-to-hand'' time is 9.8 seconds, and the average ''ventricle-to-foot'' time is about 18.5 seconds. Apparently, the speed of blood flow in arteries and veins is similar; the factors that influence the former also influence the latter.

It is of interest that an increased volume flow of blood in the arm was first noted by Hewlett and Van Zwaluwenburg,[61] in 1909, in cases of exophthalmic goiter. They stated, ''We suspect that this acceleration of the peripheral rate of blood flow is a fairly constant feature of exophthalmic goiter and roughly proportionate to the severity of the disease.'' That this statement can be applied equally well to velocity of blood flow is shown by our results. The figures indicate, also, less variability of results in hyperthyroidism than in normal subjects.

CONCLUSIONS

1. A solution of magnesium sulfate, calcium gluconate, and copper sulfate, in a physiologic solution of sodium chloride, may be used safely for determination of the speed of circulation of blood from an arm vein to the throat, hands, perineum, and feet. However, there is no evidence that the sensation of warmth produced in the throat, hands, perineum, and feet indicates the arrival of the injected solution at these areas, for there is a ''reaction time.'' In this study we have been aware of the possibility that this reaction time may be variable, and thus influence results, and that, even if it is constant, the figures we have obtained are valid only for comparative purposes. However, it appears that much information relative to the speed of blood flow in man may be gained by this method of study.

2. The average values obtained in normal subjects under controlled conditions are as follows: ''arm-to-tongue'' time, 13.7 seconds; ''arm-to-perineum'' time, 21.2 seconds; ''arm-to-hand'' time, 23.6 seconds; and ''arm-to-foot'' time, 34 seconds. The values obtained in normal subjects under uncontrolled conditions do not differ materially from those stated above, except that the average ''arm-to-foot'' time is 32 seconds.

3. The range of the ''arm-to-tongue'' time with this solution is greater than other ''arm-to-tongue'' circulation times. The range of the ''arm-to-hand'' time is greater than the range of the ''arm-to-perineum'' time. The range of the ''arm-to-foot'' time is greatest of all. These wide ranges demonstrate that the speed of blood flow varies widely in the same individual under different conditions, but under similar and basal conditions the velocity of flow is remarkably constant.

4. In cases of thromboangiitis obliterans and arteriosclerosis obliterans, the speed of blood flow to the hands and feet is usually diminished, usually depending upon the degree of vascular obliteration. Inconsistent results, however, lead us to believe that this circulation-time test cannot be used to diagnose occlusive arterial disease.

5. In cases of hyperthyroidism the speed of flow of blood is increased in the arteries as well as in the veins.

6. The "ventricle-to-perineum" circulation time has been calculated by subtracting the "arm-to-tongue" time from the "arm-to-perineum" time. Similarly, "arm-to-hand" time, minus "arm-to-tongue" time, equals "ventricle-to-hand" time, and "arm-to-foot" time, minus "arm-to-tongue" time, equals "ventricle-to-foot" time. These "times" from the "ventricle" are of course assumed, but they furnish the first means of calculating the velocity of arterial blood flow in man. In normal subjects under uncontrolled conditions, the average "ventricle-to-perineum" time is 7.3 seconds, the average "ventricle-to-hand" time is 9.8 seconds, and the average "ventricle-to-foot" time is 18.5 seconds.

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THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

II. Studies of Hypertension, of Orthostatic Hypotension, and of the Effects of Sympathectomy*

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THE solution used and the manner of measuring the speed of circulation in both the arteries and veins of man have been described in a previous communication.[1] In brief, the procedure consists in determining the time elapsing between the intravenous injection of a solution containing magnesium, calcium, and sodium salts and the occurrence of a sensation of warmth in the tongue, perineum, hands, and feet. The value and faults of the method have been described previously. The speed of flow of blood in the arteries carrying blood to the feet was estimated by subtracting the "arm-to-tongue" time from the "arm-to-foot" time, and in the arteries carrying blood to the hands by subtracting "arm-to-tongue" time from the "arm-to-hand" time.

Although our results are not in exact agreement with those published by Spier, Wright, and Saylor,[2] who introduced the use of this solution for the determination of the circulation time, we and they have established normal values for the circulation time throughout the vascular system.[1] It is the purpose of this publication to report our studies of speed of blood flow in essential hypertension, and to demonstrate the effect of sympathectomy and orthostatic hypotension on the speed of flow in peripheral arteries.

RESULTS AND COMMENT

Essential Hypertension.—Pickering[3] and Prinzmetal and Wilson[4] have shown, by means of Stewart's calorimeter and the plethysmograph, respectively, that the volume flow of blood in the forearm of the patient with essential hypertension is approximately equal to that in the patient with normal blood pressure. They made no observations on the volume flow in the foot. Steele and Kirk[5] have demonstrated that the temperature of the skin of patients suffering from arterial hypertension does not differ significantly from that of normal individuals. Williams[6] has verified these observations. These observations support indirectly the accepted evidence that there is vasoconstriction in essential hyperten-

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sion, for if this were not present the increased blood pressure would increase the flow of blood through the arterioles and thus increase the temperature of the skin.

The average "arm-to-tongue" time of 14.4 seconds for patients with essential hypertension in our observations (Table I) compares favorably

TABLE I

PATIENTS WITH ESSENTIAL HYPERTENSION

(FIFTY-EIGHT TESTS ON THIRTY-SEVEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	31	2	0	0	0	0
15-19	23	20	14	15	2	2
20-24	4	18	24	23	5	5
25-29	0	10	11	10	6	5
30-34	0	4	5	6	6	6
35-39	0	0	1	1	11	12
40-44	0	2	0	0	8	7
45-49	0	0	0	1	4	5
50-54	0	0	0	0	3	3
55-59	0	0	0	0	0	1
60-64	0	0	0	0	1	0
65-69	0	0	0	0	1	1
Blanks	0	2	3	2	11	11
Mean*	14.44±.26	22.04±.56	22.83±.45	23.36±.51	36.36±.96	36.79±1.06
Stan. dev.*	2.96	6.23	5.00	5.68	9.79	10.82

*Time in seconds.

with the time of 13.7 seconds in normal subjects. The circulation times to the perineum and hands likewise fall within the range of normal. The average "arm-to-foot" time, however (36.4 and 36.8 seconds, respectively, for the right and the left foot), is about four seconds more than the average normal under uncontrolled conditions (32.2 and 32.0 seconds, respectively), and about two seconds greater than the average normal under controlled conditions (34.3 seconds and 34.0 seconds, respectively).[1] The "ventricle-to-hand" and "ventricle-to-foot" times, since they were computed from the above, agree in a similar manner with those of the normal subjects (Table II). If the results of the fifty-eight tests on patients with hypertension, who were not under strictly basal conditions, are compared with the average normal circulation time under uncontrolled conditions, the difference is statistically significant. However, the average "arm-to-foot" time in essential hypertension is only about two seconds longer than the average "arm-to-foot" time in normal persons under controlled conditions. This difference is statistically insignificant. Whether or not the difference indicates diminished peripheral blood flow in essential hypertension, we do not know, but the figures suggest this possibility.

TABLE II

PATIENTS WITH ESSENTIAL HYPERTENSION

(FIFTY-EIGHT TESTS ON THIRTY-SEVEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	12	3	3	0	0
5-9	33	35	33	3	3
10-14	9	15	16	8	9
15-19	1	2	3	8	6
20-24	0	0	0	11	11
25-29	1	0	1	9	9
30-34	0	0	0	5	6
35-39	0	0	0	1	1
40-44	0	0	0	0	1
45-49	0	0	0	2	1
Blanks	2	3	2	11	11
Mean*	7.53	8.43	9.01	21.31	21.97

*Time in seconds.

The Effect of Sympathectomy.—At the Mayo Clinic the usual operation performed for the relief of essential hypertension consists of a two-stage resection of the splanchnic nerves with partial removal of the celiac ganglia and removal of the first and second lumbar sympathetic ganglia.[7, 8] This procedure removes sympathetic nerve control of the lower extremities. Patients on whom this operation had been performed afforded us the opportunity to determine the rapidity of the blood flow to the feet in a sympathectomized and unsympathectomized extremity simultaneously, since only one side is operated on at one time. It further enabled us to determine the rapidity of blood flow in bilaterally sympathectomized extremities.

So far as we know, the results of our study of the effect of sympathectomy on the rapidity of blood flow in man are the first to be recorded. Brown[9] has shown, however, that vasodilatation results from sympathectomy. Herrick, Essex, and Baldes[10] have demonstrated that the volume flow of blood in the femoral artery of the dog, as measured by the thermostromuhr method, is about twice as great on the sympathectomized side as on the unsympathectomized side. Freeman[11] has shown, by means of the plethysmograph, that ten days after cervicodorsal sympathectomy there is a rather marked increase in the volume flow of blood in the hand, and that this decreases as the time after operation increases. He likewise found an increased flow of blood when he blocked the sympathetic chain on one side with procaine. His final conclusions were that the increase in flow of blood to the sympathectomized hand is the result not only of the release of vasoconstrictor impulses, but also of a change in local tissue metabolism. Prinzmetal and Wilson[4] likewise observed an increased blood flow in the forearm on the sympathectomized side.

The results of twenty-five tests done on thirteen patients with essential hypertension, seven to eighteen days after the first-stage sympathectomy, are recorded in Tables III and IV. The mean "arm-to-sympathectomized foot" time was nine seconds less than the mean "arm-to-unsympathectomized foot" time, and the mean "ventricle-to-sympathectomized foot" time is also nine seconds less than the mean "ventricle-to-unsympathectomized foot" time. Unquestionably, sympathec-

TABLE III

ESSENTIAL HYPERTENSION AFTER FIRST-STAGE SYMPATHECTOMY

(TWENTY-FIVE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO SYMPATHECTOMIZED FOOT	ARM TO UNSYMPATHECTOMIZED FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	15	0	0	0	0	0
15-19	10	6	5	5	0	0
20-24	0	10	8	6	5	2
25-29	0	6	7	6	8	2
30-34	0	1	2	5	7	3
35-39	0	2	0	0	2	3
40-44	0	0	1	0	3	4
45-49	0	0	1	0	0	3
50-54	0	0	1	0	0	1
55-59	0	0	0	0	0	1
60-64	0	0	0	0	0	1
Blanks	0	0	0	3	0	5
Mean*	13.92±.25	23.88±.77	26.08±1.24	23.95±.65	30.12±.79	39.2±1.60
Stan. dev.*	1.82	5.74	9.18	4.51	5.84	10.63

*Time in seconds.

TABLE IV

ESSENTIAL HYPERTENSION AFTER FIRST-STAGE SYMPATHECTOMY

(TWENTY-FIVE TESTS ON THIRTEEN SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO SYMPATHECTOMIZED FOOT	VENTRICLE TO UNSYMPATHECTOMIZED FOOT
0-4	1	2	1	0	0
5-9	16	10	8	0	0
10-14	5	9	11	10	4
15-19	1	1	2	10	2
20-24	1	0	0	2	3
25-29	1	1	0	2	5
30-34	0	1	0	1	4
35-39	0	1	0	0	0
40-44	0	0	0	0	1
45-49	0	0	0	0	1
Blanks	0	0	3	0	5
Mean*	9.96	12.16	10.22	16.2	25.5

*Time in seconds.

tomy increases the speed with which blood flows through arteries. If one calculates the time for blood to flow from the iliac artery to the feet by subtracting "arm-to-perineum" time from "arm-to-foot" time, it appears that blood flows about twice as fast in the sympathectomized limb as it does in the normal limb.

Table V shows the results in eight individual cases. In a very few instances there was a difference of but one or two seconds, and in one case there was no difference at all. In the great majority of cases, however, the difference was large, and in some instances amounted to eighteen or nineteen seconds. The subjects who noted differences of speed of blood flow to sympathectomized and unsympathectomized legs were firm in their statements that not only was the sensation perceived in the sympathectomized leg much sooner than in the unsympathectomized leg, but that the sensation was likewise more distinct. In several cases in which "blanks" resulted before sympathectomy, the sensation was perceived distinctly after sympathectomy. The average figures of 39.2 seconds to the unsympathectomized foot from the arm, and 25.5 seconds to the unsympathectomized foot from the ventricle, in instances of unilateral sympathectomy, are both greater than the average values in the unsympathectomized extremities in normal subjects,[1] and appear to indi-

TABLE V

CIRCULATION TIMES IN CASES OF ESSENTIAL HYPERTENSION, SHOWING THE RESULTS BEFORE AND AFTER SYMPATHECTOMY

CASE	TIME OF TEST IN RELATION TO SYMPATHECTOMY	TIME IN SECONDS					
		ARM TO TONGUE	ARM TO PERI-NEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Preoperative	16	23	24	24	35	35
	9 days after left	16	23	25	31	28	26
	11 days after right	14	24	23	20	29	29
2	Preoperative	11	17	15	15	33	33
	8 days after left	12	19	23	18	31	27
	15 days after right	18	23	28	28	33	33
3	Preoperative	16	24	26	26	54	54
	7 days after right	16	23	28	30	32	50
	11 days after left	15	24	30	36	35	35
4	Preoperative	15	20	23	23	42	42
	7 days after right	13	20	22	24	24	40
	13 days after left	16	24	36	Blank	33	33
5	Preoperative	11	17	20	20	31	31
	8 days after right	12	19	24	24	26	45
	13 days after left	13	16	18	18	20	20
6	Preoperative	17	42	28	27	63	59
	11 days after right	16	30	22	26	33	49
	9 days after left	18	24	28	26	39	36
7	Preoperative	12	17	23	23	45	45
	9 days after right	13	18	17	17	23	23
	14 days after left	10	11	13	13	15	15
8	Preoperative	14	28	21	21	40	47
	18 days after right	12	39	21	26	31	36
	13 days after left	11	23	19	19	30	30

cate diversion of an unusually large amount of blood to the sympathectomized side, with consequent slowing of blood flow on the opposite side.

However, the important point is that sympathectomy of one extremity increases greatly the speed of blood flow in the arteries of that extremity. This increased speed of blood flow seems to be a direct result of vasodilatation produced by sympathectomy. An interesting observation is that in many instances blood flows faster in an extremity when it alone has been sympathectomized, than it does in the same extremity after the companion member has been sympathectomized as part of the second stage of the operation for hypertension (Table V). This may be due to the reduction of blood pressure caused by the second operation. Since the blood pressure has been reduced, blood flows less rapidly because, if the degree of vasodilatation remains roughly constant, the volume of blood flow would be directly proportional to blood pressure.

TABLE VI

ESSENTIAL HYPERTENSION AFTER BILATERAL SYMPATHECTOMY

(THIRTY-SIX TESTS ON TWENTY-THREE SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS					
	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
0-4	0	0	0	0	0	0
5-9	0	0	0	0	0	0
10-14	15	1	1	2	0	0
15-19	20	11	5	6	2	2
20-24	1	20	10	9	8	8
25-29	0	4	11	9	11	10
30-34	0	0	4	1	5	8
35-39	0	0	2	4	6	4
40-44	0	0	0	0	2	2
45-49	0	0	1	1	2	2
50-54	0	0	1	0	0	0
Blanks	0	0	1	4	0	0
Mean*	14.88±.28	21.14±.42	26.40±.88	25.03±.90	29.61±.78	29.38±.82
Stan. dev.*	2.53	3.76	7.73	7.52	6.91	7.26

*Time in seconds.

TABLE VII

ESSENTIAL HYPERTENSION AFTER BILATERAL SYMPATHECTOMY

(THIRTY-SIX TESTS ON TWENTY-THREE SUBJECTS)

TIME IN SECONDS	NUMBER OF TESTS				
	VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
0-4	11	2	4	0	0
5-9	22	12	9	9	9
10-14	3	15	13	11	10
15-19	0	3	4	7	11
20-24	0	1	1	7	4
25-29	0	0	1	1	1
30-34	0	2	0	1	1
Blanks	0	1	4	0	0
Mean*	6.25	11.54	10.50	14.72	14.50

*Time in seconds.

It is of interest that in thirty-six tests performed on twenty-three subjects who had undergone bilateral sympathectomy, "blanks" did not occur in the feet (Tables VI and VII). This but demonstrates the importance of adequate vasodilatation in the feet before the sensation of warmth produced by the injected solution can be perceived.

Orthostatic Hypotension.—Following the original observation of Brown and one of us (Adson),[12] and, more recently, those of Roth[13] and of two of us (Allen and Adson),[7, 8] that after anterior rhizotomy or bilateral subdiaphragmatic extraperitoneal resection of the splanchnic nerves, celiac ganglia, and the first and second lumbar ganglia, the blood pressure falls and the pulse rate increases when the patient stands, we desired to ascertain what effects, if any, these disturbances had on the circulation time. Five patients with orthostatic hypotension and tachycardia following operation for essential hypertension were studied (Table VIII). The test was first done with the patient in the recumbent position after a rest of half an hour. Within five to ten minutes the patient was allowed to stand, the blood pressure and pulse rate were again taken, and the test was repeated with the arm at the patient's side (Table VIII).

TABLE VIII

CIRCULATION TIME IN CASES OF ORTHOSTATIC HYPOTENSION RESULTING FROM SYMPATHECTOMY FOR HYPERTENSION

CASE	BLOOD PRESSURE	PULSE RATE	POSITION OF BODY	TIME IN SECONDS					
				ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	180/122	92	Lying	13	21	23	23	27	27
	102/82	128	Standing*	55	61	61	61	71	71
2	156/112	84	Lying	15	20	25	25	31	31
	112/88	124	Standing	29	36	48	48	Blank	Blank
3	152/94	92	Lying	13	17	19	19	25	25
	84/60	128	Standing	16	20	28	28	32	32
4	106/64	100	Lying	13	16	18	18	20	20
	60/40	96	Standing	22	25	31	31	62	62
5	134/84	92	Lying	10	15	17	17	22	22
	74/60	132	Standing	18	30	24	24	48	48

*No reactions at end of 35 seconds. Patient then lay down because of vertigo and faintness, reactions occurring from time of injection.

Two patients with spontaneous orthostatic hypotension were studied, but no reactions occurred within two minutes when the patients were standing, and consequently had marked decreases in blood pressure. Surprisingly, when they lay down again, reactions produced by the injected solution occurred within about the same time after lying down as they did after the moment of injection when the injections were made originally with the patients lying down. These limited observations on spontaneous orthostatic hypotension indicate that the blood was almost entirely stagnant in the veins when these two patients were standing, and explain the marked weakness which prevented their standing more than two or three minutes.

As far as we have been able to determine, the circulation time in orthostatic hypotension has not been extensively studied. Prinzmetal and Wilson,[4] by the use of the plethysmograph, found no change in the volume flow of blood in the arm in a case of postural hypotension with the patient in either the lying or standing position. The results of our study of orthostatic hypotension resulting from sympathectomy indicate that the "arm-to-tongue," "arm-to-hand," "arm-to-perineum" and "arm-to-foot" times are all prolonged when the patient stands and the blood pressure is reduced (Table VIII). The marked slowing of the circulation in these cases is due to slowing of both venous and arterial circulation. For example, in Case 5, the "arm-to-tongue" time was increased only eight seconds, while the "ventricle-to-foot" time was increased eighteen seconds when the patient stood.* In this instance the speed of blood flow was decreased in both arteries and veins.

CONCLUSIONS

1. The circulation time in cases of essential hypertension falls within normal limits, except that the "arm-to-foot" time is slightly increased. We do not know whether or not this indicates diminished blood flow to the feet in essential hypertension, but the figures suggest such a possibility.

2. Unilateral sympathectomy for hypertension decreases the circulation time from the arm to the sympathectomized foot to a value about nine seconds less than it is to the unsympathectomized foot. After bilateral sympathectomy for hypertension the average "arm-to-foot" circulation time, as determined by thirty-six tests on twenty-three subjects, is about 29.5 seconds, or about three to five seconds faster than normal. This increased speed of flow is attributed directly to vasodilatation.

3. In spontaneous orthostatic hypotension there is a marked increase in the "arm-to-tongue" time and in the "arm-to-foot" time when the patient stands. In orthostatic hypotension which results from extensive sympathectomy for essential hypertension, the decrease in speed of flow of blood occurs in the peripheral veins and pulmonary circulation, as well as in the peripheral arteries.

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THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

III. The Influence of Temperature of the Skin, Digestion, Posture, and Exercise*

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THE study of the effect of physiologic processes on the rate of circulation of blood in man has been limited almost entirely to that in the veins, since there was no suitable method for determining the speed of blood flow in arteries until Kahler[1] described his method in 1929. A similar method was described by Spier, Wright, and Saylor[2] in 1936. They injected intravenously a solution of calcium, magnesium, and sodium, and determined the time elapsing between injection and the occurrence of a warm sensation in the tongue, perineum, hands, and feet. We have used this method and have reported the results of our studies in normal subjects and in subjects with various pathologic conditions.[3, 4] As stated in a previous publication, we believe that information regarding speed of flow in arteries can be secured by subtracting the "arm-to-tongue" time from the "arm-to-foot" time, the result being a figure which indicates roughly the "ventricle-to-foot" time, that is, the time required for blood to flow from the left ventricle to the foot. "Ventricle-to-hand" time can be estimated by a similar calculation.

The method we have used permits investigation of the influence of temperature of the skin, digestion, posture, and exercise on the speed of flow of blood in the arteries.

EFFECT OF TEMPERATURE OF THE SKIN ON SPEED OF CIRCULATION

Effect of Environmental Temperature.—The effect of skin temperature on peripheral volume flow of blood was demonstrated by Hewlett and Van Zwaluwenburg,[5, 6] in 1910, by Stewart,[7, 8] in 1911, and by Freeman,[9] in 1935.

In our studies the patient was allowed to remain at rest for at least one hour, or longer, if necessary, until his blood pressure, pulse rate, and skin temperature had attained a basal level. A thermocouple was attached to each great toe and to the third finger of each hand, and the

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TABLE I

EFFECT OF SKIN TEMPERATURE ON CIRCULATION TIME

EXP.	PROCEDURE	ROOM TEMP. (° C.)	SKIN TEMPERATURE (° C.)				TIME IN SECONDS					
			R^1 TOE	L^1 TOE	R^3 FINGER	L^3 FINGER	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Control	25.0	24.0	25.7	30.3	32.0	12	18	24	22	35	38
	*	26.2	33.1	34.7	36.1	36.3	11	16	19	19	25	28
2	Control	25.2	27.2	27.4	30.3	29.7	12	18	22	20	41	37
	†	18.8	18.5	18.5	18.7	19.2	14	21	Blank	36	Blank	Blank
	*	20.0	37.0	37.4	38.8	38.8	11	16	18	17	23	26
3	Control	25.9	25.1	25.2	30.5	29.8	12	17	23	26	42	37
	*	26.4	36.5	37.0	37.1	34.9	11	16	17	18	21	22
4	Control	25.2	26.5	26.3	27.4	27.0	17	30	33	37	52	43
	†	18.8	20.0	20.7	19.5	19.5	17	27	44	Blank	Blank	Blank
	*	19.5	38.5	32.6	35.7	37.0	16	25	19	26	39	32
5	Control	23.9	22.7	22.7	20.0‡	20.0‡	11	14	16	20	28	28
	*	23.5	35.2	35.4	36.6	36.6	10	15	12	16	22	23

*Vasodilatation induced by baker over body.

†Vasoconstriction induced by lowered environmental temperature.

‡Hands placed in ice water at 6° C. for one minute; thirteen minutes before readings were recorded.

temperature of the skin ascertained by means of the Sheard electric thermometer.[10] As soon as the control test had been obtained the patient was transferred to a room the temperature of which was 5 to 7° C. colder (Cases 2 and 4 of Table I). When the patients were subjected to the low environmental temperature, sensations usually provoked by the injected solution were felt only in the left hand (Case 2) and right hand (Case 4), and in both instances the circulation time was increased. As we shall show later, failure to perceive sensation is due to decreased cutaneous temperature.

Effect of Reflexly Induced Vasodilatation.—Vasodilatation was produced by a body baker after a suitable control period, during which a test was performed. Skin temperatures were recorded every minute, and after vasodilatation had occurred the test was repeated (Table I). In every instance, with the exception of the "arm-to-perineum" time in Case 5, the speed of the blood flow was increased. Especially was this so in the case of the feet, and in cases in which "blanks" had occurred with a lowered environmental temperature there were none when sufficient vasodilatation had been produced.

*Explanation of So-Called Blanks.**—The "blanks" which occasionally occurred in this study disturbed us. They were especially frequent in the feet. Some of them were due to confusion on the part of the patient, who would forget to report all regions; in these instances repetition of the test in five to ten minutes might produce the reaction, but there still seemed to be some other factor that played a role in the occurrence of "blanks." This factor was apprehended gradually as more and more tests were done. It was noted that on especially warm days there were relatively few "blanks"; that on cold days and in a cold

TABLE II

EFFECT OF VASODILATATION PRODUCED BY APPLICATION OF EXTERNAL HEAT ON CIRCULATION TIME

(EXPLANATION FOR THE OCCURRENCE OF "BLANKS")

EXPERIMENT	SKIN TEMPERATURE (° C.)		TIME IN SECONDS	
	R[1] TOE	L[1] TOE	ARM TO R. FOOT	ARM TO L. FOOT
1	23.4	23.4	Blank	Blank
	34.3	35.7	44	44
2	24.3	24.3	Blank	Blank
	40.1	40.4	27	27
3	30.0	28.7	Blank	Blank
	35.0	34.5	32	28
4	24.0	24.2	Blank	Blank
	38.7	38.2	25	25
5	24.0	24.2	Blank	Blank
	35.4	37.7	20	20

*When no sensation is perceived in a foot, for example, after the solution is injected, the result is recorded as "blank."

room they occurred rather frequently. This led to the observation that skin temperature was important in the frequency of occurrence of "blanks." Whenever "blanks" occurred, vasodilatation was induced by direct application of radiant heat to the feet and legs. After suitable warming of the skin, sensation was perceived routinely (Table II).

The tonic state of the arterioles in the feet seems to have more of a bearing on the perception of the sensation than it does in the hands. "Blanks" occur relatively rarely in the hands and perineum, but in the feet they are met with in 19 to 20 per cent of instances. There seem to be two reasons for this. The feet are usually colder than the hands, and the longer circuit to the feet may cause enough dilution of the solution so that a sufficiently high concentration of the solution does not reach them.

Vasodilatation in One Extremity.—Since unilateral sympathectomy causes blood to flow much faster[4] in the sympathectomized leg than it does in the normal one, we investigated the effect of unilateral vasodilatation induced by heat. The application of external heat to one extremity produces vasodilatation not only in that extremity, but also reflexly in the other extremities. To overcome this reflex vasodilatation, an ordinary blood pressure cuff was placed around the thigh of the leg to which external heat was to be applied, and was inflated to the level of the diastolic pressure in order that the venous return might be obstructed.[11] A baker was then placed over the leg until there was a difference in the cutaneous temperature of the two legs of at least 5° C. The cuff was then deflated and the test performed at once. These studies indicate conclusively that an increased cutaneous temperature is associated with increased speed of flow (Table III). However, the difference in temperature of the skin of the two extremities was not proportional to the difference in circulation time.

TABLE III

EFFECT OF VASODILATATION IN ONE LEG ON CIRCULATION TIME

CASE	TEMPERATURE OF SKIN OF TOES (° C.)		ARM-TO-FOOT CIRCULATION TIME (IN SECONDS)	
	RIGHT	LEFT	RIGHT	LEFT
1	29.5	38.0	49	37
2	24.5	31.9	73	51
3	29.4	35.6	47	43
4	27.7	32.8	46	38
5	28.2	34.3	42	30

EFFECT OF TACHYCARDIA ON SPEED OF BLOOD FLOW

Atropine sulfate, in doses of $\frac{1}{50}$ and $\frac{1}{60}$ grain (0.0013 and 0.0011 gm.), administered subcutaneously, induced tachycardia; the maximum occurred from one to two hours after injection (Table IV). Changes

TABLE IV

EFFECT OF TACHYCARDIA ON CIRCULATION TIME*

EXP.	PROCEDURE	PULSE	SKIN TEMPERATURE (° C.)				TIME IN SECONDS					
			R^1 TOE	L^1 TOE	R^3 FINGER	L^3 FINGER	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Control	56	23.5	23.5	24.4	24.7	13	18	21	23	30	30
	†	104	25.7	25.8	30.2	30.4	11	14	17	16	21	21
2	Control	60	31.6	30.7	32.5	31.7	12	20	22	19	28	28
	†	96	33.9	33.5	34.7	35.0	12	16	15	14	18	18
3	Control	60	31.8	31.1	32.0	31.1	10	23	23	23	29	31
	†	88	30.3	28.6	30.8	31.4	10	20	21	21	25	25
4	Control	68	26.5	26.2	26.5	25.9	14	27	30	31	39	37
	†	100	28.4	27.1	28.1	26.5	10	16	23	21	27	27
5	Control	80	29.7	30.1	32.7	34.0	13	21	22	17	35	39
	†	96	32.3	31.8	34.0	34.8	14	20	19	19	29	27
6	Control	80	26.5	27.8	30.0	30.0	13	22	20	20	36	34
	†	100	26.1	27.4	32.7	34.5	12	22	20	25	34	36

*Experiments carried out in constant-temperature room.

†One to two hours after the subcutaneous injection of atropine sulfate.

in blood pressure were minimal. The temperature of the skin of the fingers and toes usually increased somewhat. If we disregard increase in cutaneous temperature as a cause for changed speed of circulation,* tachycardia induced by atropine increased the speed of flow in all instances except the "arm-to-tongue" time and "arm-to-left-hand" time in experiment 5, the "arm-to-perineum," "arm-to-right-hand," "arm-to-left-hand," and "arm-to-left-foot" time in experiment 6, and the "arm-to-tongue" time in experiments 2 and 3. Blumgart and Weiss[12] also found that the rate of blood flow from arm to arm increased when there were conspicuous increases of the pulse rate.

EFFECT OF EXERCISE ON SPEED OF BLOOD FLOW

Ellis,[13] in 1932, showed that the arm-to-carotid-sinus circulation time in five cases, computed from his tables, was decreased an average of 6.3 seconds after the subjects had exercised on a bicycle. In our studies the circulation time was first determined with the patient at rest. He then ascended and descended the stairs (described by Master and Oppenheimer[14]) for one minute, at the end of which time he was allowed to lie down and the test was immediately repeated. In almost all instances the speed of flow was increased (Table V). Calculations of speed of

TABLE V

EFFECT OF EXERCISE ON CIRCULATION TIME

CASE		PULSE	TIME IN SECONDS					
			ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Before exercise	88	10	15	18	17	22	20
	After exercise	140	8	11	14	17	23*	20
2	Before exercise	80	12	18	19	19	31	31
	After exercise	120	9	14	16	17	21	21
3	Before exercise	80	11	16	20	20	26	26
	After exercise	104	4	7	13	13	22	22
4	Before exercise	76	13	26	22	20	47	33
	After exercise	120	11	14	18	18	31	31
5	Before exercise	84	11	14	19	19	41	41
	After exercise	120	11	17*	22*	23*	32	38
6	Before exercise	80	12	18	19	19	31	31
	After exercise	124	9	14	16	17	21	21

*Indicates prolongation, rather than shortening, of circulation time as a result of exercise.

blood flow from "ventricle to foot," as described in a previous communication, indicate that the rate of flow in the peripheral arteries is increased as a result of exercise. Perhaps all of the increased speed of flow is due to increased cardiac output, associated with tachycardia.

*This is not allowable, of course, since previous studies indicate that cutaneous temperature increases speed of flow, but in these studies changes in skin temperature were usually minimal.

TABLE VI

EFFECT OF DIGESTION ON CIRCULATION TIME

EXP.	PROCEDURE	SKIN TEMPERATURE (° C.)				TIME IN SECONDS					
		R^1 TOE	L^1 TOE	R^3 FINGER	L^3 FINGER	ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOOT	ARM TO L. FOOT
1	Control	27.6	30.9	32.5	32.7	13	19	22	20	39	31
	1 h. 35 m.*	31.0	31.6	34.4	34.8	12	20	20	19	31†	25
2	Control	28.6	29.8	31.3	31.1	12	22	23	23	31	31
	2 h. 35 m.*	31.1	32.3	34.5	33.4	11	19	19	16	28	39†
3	Control	31.3	32.0	32.0	33.3	22	30	36	36	51	51
	1 h. 58 m.*	32.2	32.6	34.0	34.2	21	29	27	27	46	46
4	Control	29.7	27.3	31.3	32.1	18	26	32	32	46	46
	2 h. 20 m.*	32.2	32.8	31.4	32.5	14	22	25	25	35	35
5	Control	28.0	27.2	31.5	31.6	11	14	19	19	41	41
	2 h. 45 m.*	31.0	31.2	31.7	31.3	14	20	26	22	38	41

*After large meal.
†Cuff around leg inflated to the level of diastolic pressure.

EFFECT OF DIGESTION ON SPEED OF BLOOD FLOW

Herrick, Essex, Mann, and Baldes,[15] in 1934, using a thermostromuhr, showed that the volume flow of blood in the carotid, femoral, and mesenteric arteries of dogs was increased during digestion. Their results were confirmed by McCracken, Essex, and Sheard,[16] who injected small quantities of the disintegration products of radon (radium emanation) into the jugular veins of animals and noted the time required for them to pass to a point in the femoral artery lying in the adductor canal. They found that the circulation time in dogs was decreased 12.9 to 45.5 per cent during the course of digestion.

The subjects of our observations were placed in a constant-temperature room, without breakfast, and rested for at least an hour and a half, or until their blood pressure, pulse rate, and skin temperatures were stable. A control circulation time was then obtained. They were then allowed to eat a large breakfast, consisting of orange juice, three fried eggs, bacon, buttered toast, a sweet roll, and milk. The blood pressure, pulse rate, and skin temperatures were then taken as often as seemed necessary. The height of digestion, which was judged by the maximal increase in skin temperature, occurred from an hour and a half to two hours and a half after eating. The blood pressure changed insignificantly, the heart rate increased four to twelve beats per minute in different subjects, and the cutaneous temperatures increased somewhat.

TABLE VII

EFFECT OF POSTURE ON CIRCULATION TIME

CASE		PULSE	TIME IN SECONDS					
			ARM TO TONGUE	ARM TO PERINEUM	ARM TO R. HAND	ARM TO L. HAND	ARM TO R. FOO	ARM TO L. FOOT
1	Lying	80	13	18	24	24	27	27
	Standing	96	12	17	24	24	29	29
2	Lying	78	12	20	24	23	28	28
	Standing	92	15	24	27	35	49	50
3	Lying	72	14	19	20	23	25	25
	Standing	104	14	19	20	23	31	31
4	Lying	64	12	19	14	17	24	25
	Standing	92	13	18	21	10	31	31
5	Lying	76	10	14	12	17	25	25
	Standing	104	12	19	21	17	29	29
6	Lying	68	15	25	28	28	45	45
	Standing	68	19	25	48	48	Blank	Blank
7	Lying	92	12	16	23	18	31	31
	Standing	100	11	17	18	18	30	30
8	Lying	88	14	19	23	23	33	33
	Standing	96	13	21	23	23	38	38
9	Lying	80	20	27	45	45	51	51
	Standing*	92						
	†		103	109	Blank	Blank	112	112
	‡		13	19	Blank	Blank	22	22

*No reaction for ninety seconds, lay down with reactions occurring.
†From time of injection.
‡From time of lying down.

The results are given in Table VI. In all experiments, except the fifth, it will be seen that the speed of the blood flow was usually increased as a result of digestion.

EFFECT OF POSTURE ON SPEED OF BLOOD FLOW

The effect of posture on the speed of venous circulation has been fairly well studied,[17-20] and the results indicate that the upright posture decreases the rate of venous blood flow. This has been attributed to the effect of gravity.

In our studies, control circulation times were first obtained after the patient had lain for a sufficient length of time to allow his pulse rate to approach a basal level. He was then allowed to stand still for five to ten minutes before the second test was done. The results of the study are shown in Tables VII and VIII. The effect of the upright posture on "arm-to-tongue" time was variable (Table VII). The "arm-to-feet" time was increased, except in Case 7. The "arm-to-hand" time was not consistently changed by the upright posture. Calculation of the "ventricle-to-feet" time, as described previously, indicates regular slowing of the arterial circulation, apparently as a result of vasoconstriction resulting from the upright posture (Table VIII).

TABLE VIII

EFFECT OF POSTURE ON CIRCULATION TIME

CASE		TIME IN SECONDS				
		VENTRICLE TO PERINEUM	VENTRICLE TO R. HAND	VENTRICLE TO L. HAND	VENTRICLE TO R. FOOT	VENTRICLE TO L. FOOT
1	Lying	5	11	11	14	14
	Standing	5	12	12	17	17
2	Lying	8	12	11	16	16
	Standing	9	12	20	34	35
3	Lying	5	6	9	11	11
	Standing	5	6	9	17	17
4	Lying	7	2	5	12	13
	Standing	5	8	6	18	18
5	Lying	4	2	7	15	15
	Standing	7	9	5	17	17
6	Lying	10	13	13	30	30
	Standing	6	29	29	Blank	Blank
7	Lying	4	11	6	19	19
	Standing	6	7	7	19	19
8	Lying	5	9	9	19	19
	Standing	8	10	10	25	25
9	Lying	7	25	25	31	31
	Standing* †	6	Blank	Blank	9	9

*No reaction for ninety seconds, lay down with reactions occurring.
†From time of lying down.

CONCLUSIONS

1. The velocity of the flow of blood in the peripheral arteries of man is dependent on cutaneous temperature. Increasing the temperature

increases speed of flow, and decreasing cutaneous temperature decreases speed of flow.

2. The speed of blood flow is increased during digestion.

3. The speed of circulation to the feet is decreased when a patient stands erect. This is apparently due to vasoconstriction which occurs on standing.

4. Exercise increases speed of circulation.

5. Marked increases in the pulse rate, without affecting the blood pressure significantly, and with little or no effect on the temperature of the skin, increase the velocity of blood flow. Minor variations in the pulse rate seem to have no effect on the velocity of flow.

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THE RATE OF THE CIRCULATION IN THE ARTERIES AND VEINS OF MAN

IV. An Error in the Sodium Cyanide Method of Determining Speed of Venous Blood Flow*

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MANY methods have been introduced for studying the rate of circulation of blood. In this study, attention will be directed only toward those methods which have as their signal reaction a characteristic taste in the mouth, and the sodium cyanide method, which causes a sudden deep inspiration by stimulation of the carotid sinus. In other words, the circuit involved includes an arm vein, the right side of the heart, the pulmonary system, the left side of the heart, the aorta, and vessels leading to the carotid sinus and tongue.

In the course of other studies, our attention was directed toward the fact that reports of those methods which utilize as their end point a characteristic taste in the mouth indicated that these methods give shorter circulation times than those reported for a method which depends on stimulation of the carotid sinus, that is, the sodium cyanide method. And yet, the distance to the tongue from an arm vein by way of blood vessels is greater than the distance to the bifurcation of the common carotid artery, which is the site of the carotid sinus. It is, therefore, our purpose in this study to present, by injecting appropriate solutions intravenously, a study of this difference in time required to stimulate the end organs in the tongue and that required to stimulate the carotid sinus.

The normal circulation times, as found by various observers, are given in Table I. In every instance except one,[1] the average "arm-to-carotid" circulation time, as measured by the sodium cyanide method, is greater than the "arm-to-tongue" circulation time determined by any one of the other methods. Wood,[2] using the decholin method on twenty-five subjects, obtained an average of 13.5 seconds, including the injection time. Using the sodium cyanide method on ten subjects, he obtained an average of 15.7 seconds. Gargill,[1] using the decholin method on fifty normal subjects, obtained an average of 15.9 seconds, not including the injection time of 1 to 2 seconds. Using the sodium cyanide method on fifteen normal subjects, he obtained an average of 15.6 seconds. So far

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as we know, Gargill's observations are the only ones in which a close correspondence has been found between the "arm-to-tongue" and "arm-to-carotid sinus" circulation time.

PROCEDURE

The method we have used for measuring the "arm-to-tongue" circulation time has been described previously.[3] In brief, it consists in determining the time elapsing between the intravenous injection of a solution containing the salts of magnesium, calcium, and sodium into a vein at the elbow, and the occurrence of a warm sensation at the tongue or throat. To ascertain how closely the sudden gasp produced by the action of sodium cyanide on the carotid sinus synchronizes with the sensation of warmth produced by the action of magnesium, calcium, and sodium on the reactive organs in the tongue, we mixed the solution described with a solution of sodium cyanide, after animal experiments had indicated that such a mixture could be injected safely.

The mixture, which consisted of 7 mg. of sodium cyanide dissolved in 0.5 c.c. of distilled water and 2 c.c. of the solution we have been using for determining speed of circulation, was injected into a vein at the elbow in the usual manner. The time elapsing between the injection and the gasp, and that elapsing between the injection and the perception by the patient of warmth in his mouth were carefully noted.

TABLE I

NORMAL CIRCULATION TIME FROM INJECTION OF SOLUTION INTO A VEIN OF THE ARM TO REACTION PRODUCED BY STIMULATION OF CAROTID SINUS (SODIUM CYANIDE METHOD) OR OF NERVES OF THE TONGUE (OTHER METHODS)

OBSERVERS	YEAR	METHOD	RANGE (SEC.)	AVERAGE (SEC.)
Fishberg, Hitzig and King[4]	1933	Saccharin	9-16	
Wohl and Ettelson[5]	1935	Saccharin	7.4-20	13.3
Drennan[6]	1936	Saccharin	12-18	
Webb, Sheinfeld and Colin[7]	1936	Saccharin	6-18	10.7
Baer and Slipakoff[8]	1938	Saccharin	9-16	12.6
Hurst and Brand[9]	1936	Saccharin	12-16	12.7
Kahler[10]	1929	Calcium chloride	9-15	
Leschke[11]	1931	Calcium chloride	9-13	
Berinskaya and Meerzon[12]	1935	Calcium chloride	10-15	11.5
Goldberg[13]	1936	Calcium gluconate	10-16	12.5
Spier, Wright and Saylor[14]	1936	Calcium, magnesium and sodium salts	7-22	14.6
Kvale and Allen[3]	1939	Calcium, magnesium and sodium salts	9-23	13.7
Baer and Slipakoff[8]	1938	Calcium gluconate	9-16	12.7
Winternitz, Deutsch and Brüll[15]	1931	Decholin	8-14	
Gargill[1]	1933	Decholin	15-20	15.9*
Tarr, Oppenheimer and Sager[16]	1933	Decholin	10-16	13.0
Wood[2]	1936	Decholin	9.5-18	13.5†
Alvarez[17]	1933	Endoidine	12-14	
Neurath[18]	1937	Magnesium sulfate	11-17	
Robb and Weiss[19]	1933	Sodium cyanide	9-21	15.6
Gargill[1]	1933	Sodium cyanide	12.5-18	15.6
Wood[2]	1936	Sodium cyanide	13-19.5	15.7
Kopp[20]	1936	Sodium cyanide	14-20.5‡	

*Injection time not included.

†Injection time included.

‡Includes range in twelve of fifteen patients. In remaining three cases, circulation time was prolonged, for which adequate reasons were given.

RESULTS

The results of eleven such experiments, performed on four subjects, are shown in Table II. In every instance, the sensation of warmth in the tongue was experienced first, and the gasp appeared as the sensation of warmth was subsiding or had disappeared. The results were unquestionable. The subjects on whom these tests were performed and the individuals observing the experiments were impressed by the constancy with which the sensation of warmth in the mouth preceded the gasp. A mean difference of 3.4 seconds was found, with a range of 1 to 5 seconds. In other words, the sensation of warmth in the tongue appeared, on the average, 3.4 seconds sooner than the sudden gasp.

TABLE II

COMPARISON OF CIRCULATION TIMES FROM ARM TO CAROTID SINUS (SODIUM CYANIDE) AND FROM ARM TO TONGUE

SUBJECT	TIME IN SECONDS	
	ARM TO TONGUE	ARM TO CAROTID SINUS
1	11	14
	13	18
2	15	19
	14	18
3	13	16
	14	19
4	7	11
	11	14
	11	13
	14	17
	13	14
Mean	12.36	15.73

Mean difference 3.37.

COMMENT

Mention has already been made of the circulation times between arm and tongue and arm and carotid sinus, as noted by various observers and by us. Attention has been drawn to the fact that in all reports in the literature except one, the "arm-to-tongue" circulation time has been found to be shorter than the "arm-to-carotid" circulation time. And yet, the solution must traverse a greater distance to reach the mouth than the carotid sinus.

It is probable that the solution of sodium cyanide reaches the bifurcations of the carotid arteries before the solution of magnesium and calcium salts reaches the mouth, since both traverse the same pathway.* Assuming that this is true, there appear to be only two explanations for the longer sodium cyanide time. Either the sodium cyanide stimulates the carotid sinus only when all of it has arrived at the bifurcation of the carotid artery, while the first of the magnesium-calcium solution

*It is highly improbable that the solution of sodium cyanide "lags" in the blood stream while the solution of calcium and magnesium salts flows as fast as the blood.

arriving at the site of stimulation is sufficient to call forth a response, or the reaction time of the pathway affected by the sodium cyanide is longer. It seems unlikely that any two pathways involved, each culminating in a motor response, would show a discrepancy of three seconds in reaction, or traversal, time. It therefore seems probable that a summation effect is required for the sodium cyanide to act on the carotid sinus.

The sodium cyanide method has been recommended because it requires no cooperation on the part of the patient, yet it can now be demonstrated that it is less accurate than the subjective method which we and other investigators have used, as far as determination of circulation time is concerned. We do not wish to minimize the value of the sodium cyanide method, for normal values for it have been established and the error in it seems relatively constant. Hence the method may be used freely for comparative purposes if it is remembered that it has an inherent error. Whatever the explanation, our studies show conclusively that the solution which we have used in our investigations gives more reliable information about the actual speed of flow of blood from an arm to the tongue than sodium cyanide does when used to determine the speed of blood flow from an arm to the carotid sinus.

CONCLUSIONS

By mixing a solution of sodium cyanide with a solution of magnesium, calcium, and sodium salts, and injecting this mixture into a cubital vein, it has been shown that there is an error in the sodium cyanide method of determining speed of blood flow. The time required for blood to flow from an arm vein to the carotid sinuses, as ascertained by injection of a solution of sodium cyanide, appears to be about three seconds more than the time actually required for blood to flow from an arm vein to the carotid sinuses.

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ANEURYSM OF THE PULMONARY ARTERY

A Review of the Literature and Report of Two New Cases

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ANEURYSM of the trunk or of the main branches of the pulmonary artery is rare. Among 37,757 consecutive autopsies reviewed by three groups of workers[1-3] not a single case was encountered; no examples were observed among 1,671 cases of aneurysm.[3-5] However, Crisp[6] noted two instances while compiling a series of 530 aneurysms, although he found no record of involvement proximal to the bifurcation of the main trunk. Although the combined studies of Henschen,[7] D'Aunoy and von Haam,[8] and Jennes[1] would indicate that 122 cases of aneurysm of the pulmonary artery had been reported up to 1936, exclusion of instances of dilatation of the pulmonary artery and inclusion of cases previously overlooked would raise the number to a total of 139. Up to 1906, in only two cases among forty-six was the correct diagnosis made ante mortem,[9, 10] but progressive improvement in roentgenologic methods has raised the number of correct diagnoses to twelve of the 122 known in 1936, and to twenty-eight at the present time (September, 1939).

If discussion is limited to cases observed since 1833 in which the diagnosis was confirmed by necropsy, 111 examples of aneurysm of the trunk or of one or both main branches are available for analysis. The figure is obtained by using the statistics of D'Aunoy and von Haam[8] (omitting cases 16 and 76 of their report, since the smaller branches were affected), and adding all other cases reported up to the present time (September, 1939). Dissecting aneurysms not arising as a result of aneurysm, and simple diffuse dilatation, irrespective of cause or size, have been excluded.

The term "pulmonary aneurysm" is here limited to those dilatations which are the result of, or associated with, actual damage to one or more coats of the vessel. Justification for the inclusion of any given case rests on autopsy (Table I) or reasonably positive clinical (Table II) findings.

All of the patients included in the latter group were still living when the cases were reported. The possibility of confusion with some other lesion is therefore not entirely eliminated. However, careful clinical study of these cases has been the means of developing useful criteria for the recognition of disease of the pulmonary artery, and for that reason a collective analysis seems to be warranted.

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Age and Sex.—Males (fifty-five patients) and females (fifty-three patients) were equally affected among the 108 patients whose sex was mentioned. This 1:1 ratio is quite in contrast to the ratio of 5.6 males to 1.0 females observed in cases of aortic aneurysm.[11] The mean age for the entire series was 37.7 years, of the females 38.7, and of the males 37.2. The extremes of age were four years[12] and eighty-two years;[13] both of these patients were females, and the lesions were ascribed to congenital malformations.

The age and sex distribution in 108 cases is shown by the following figures:

Age	0 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 and over	Total
Male	4	14	7	14	12	2	2	55
Female	9	9	12	7	7	1	8	53
Total	13	23	19	21	19	3	10	108

In addition to indicating the equal sex distribution, the figures are striking in another respect. Thirty-four per cent of pulmonary artery aneurysms occur before the age of 30, while only 16 per cent of aortic aneurysms are encountered in this period;[11] while the sexes are equally affected in the former, 88 per cent of the latter are noted in males. A similar incidence of pulmonary aneurysm is observed between the ages of 30 and 60 (38 per cent), whereas 63 per cent of aortic aneurysms occur during this period;[11] although males are slightly predominant in the former, aortic aneurysm is eleven times more common in males in this age period. Accordingly, the analysis of age and sex incidence suggests that different etiologic, functional, and anatomic factors are operative in the two types of aneurysm.

Location and Type of Aneurysm.—The trunk of the artery was involved in eighty-nine of 111 cases (trunk alone, seventy-five, trunk and both main branches, nine, trunk and left branch, five); these figures support Costa's[14] contention that the trunk is affected in approximately 85 per cent of the cases. Among trunk aneurysms, thirty-six were fusiform, forty-one were saccular, and the form of the remainder was not specified. The location of the aneurysm in the absence of trunk involvement was as follows: both branches, three; right branch, nine; left branch, ten. Since no fusiform aneurysms of the left branch have been reported, saccular aneurysms predominate in the branches (thirteen left, three right). This may account for the observation that left branch aneurysms are seen more commonly than right.[15]

Etiology.—The observation that the pulmonary artery is thinner than other vessels of equal caliber, and that the elastic and muscular component of the media, especially along the anterior and lateral walls, is less abundant, have led to a comparison of its structure with that "of a vein."[6] Moreover, the pulmonary artery seems to partake of the high degree of distensibility which characterizes the lung vessels, presumably

TABLE I*

TABULATION OF FINDINGS IN TWENTY-SIX AUTOPSY CASES OF ANEURYSM OF THE PULMONARY ARTERY

NO.	YEAR	AUTHOR	AGE	SEX	MORPHOLOGY	ETIOLOGY	COINCIDENTAL PATHOLOGIC FINDINGS IN CIRCULATORY SYSTEM
1	1854	Triebel[43]	50	M	Saccular aneurysm of trunk, size of a filbert.	Sclerosis	Sclerosis pulmonary artery. No dilatation r. ventricle.
2	1863	Touzé[33]	49	M	Fusiform aneurysm of trunk.	?	A. dissected along artery to second branch. Death by rupture.
3	1902	Mantovani[44]	25	M	Fusiform aneurysm of trunk.	Rheumatic infection; congen. def.	Mitral stenosis. Congenital stenosis pulmonary artery. Rupture of sac.
4	1904	Ekkert[45]	42	F	Fusiform aneurysm of trunk with thin, sclerotic wall.	Syphilis; sclerosis (?)	Widespread sclerosis pulmonary artery and aorta.
5	1904	Vincenzo[46]	54	M	Fusiform aneurysm of trunk and both branches.	Syphilis; sclerosis (?); cong. def. (?)	Dilatation and sclerosis of aorta. Death by dissection and rupture.
6	1905	Arnheim[47]	5	M	Fusiform aneurysm of trunk.	Infection	Congen. stenosis pulmonary valve. Pericarditis. Pulmonary tbc.
7	1917	Reimann[48]	50	F	Fusiform aneurysm of trunk, 18 cm. in circumference.	Syphilis	Syphilitic mesarteritis with multiple pulmonary infarction.
8	1918	Boinet[49]	--	--	Saccular aneurysm of trunk.	Infection	Aneurysm sigmoid valve of pulmonary artery with endocardial vegetations.
9	1924	Terplan[50]	55	F	Circumscribed aneurysm of trunk.	Congen. def.; infection	Open ductus arteriosus. Streptococcic endocarditis. Polypous thromboendarteritis of stem of pulmonary artery.
10	1927	Laubry and Thomas[29]	45	F	Sacciform aneurysm of trunk.	Syphilis	Generalized syphilitic arteritis.
11	1928	Salzer[51]	60	F	Circumscribed, thrombosed aneurysm of rt. main branch.	Syphilis	
12	1930	Plenge[52]	40	M	Saccular aneurysm of trunk.	Syphilis	Marked "lipoid" sclerosis pulmonary artery and aorta.
13	1932	Esser[53]	25	F	Sacciform aneurysm of trunk.	Congen. def.	"High-grade" hypoplasia entire vascular system. "Cavernous" pulmonary tbc.
14	1933	Käppeli[54] and Lüdin[55]	71	F	Saccular aneurysm of trunk.	Sclerosis	Pulmonary emphysema. Secondary sclerosis pulmonary artery.
15	1933	Karsner[26]	28	F	Fusiform aneurysm of trunk.	Syphilis	Mesaortitis with multiple, small, saccular aneurysms.

*Patterned after table of D'Aunoy and von Haam.[3]

16	1934	Joules[56]	37	F	Fusiform aneurysm of trunk and both branches.	Congen. def.	Hypoplasia of aorta. Interauricular and interventricular septal defects. Open ductus arteriosus.
17	1934	Holst[57]	28	F	Aneurysm of trunk.	Infection	Hyperthyroidism. Rheumatic pancarditis with adhesive pericarditis.
18	1934	Scott[77]	48	M	Saccular aneurysm in each main branch.	Syphilis (?); sclerosis (?)	Moderate coaretation of aorta. Calcified plaques on pulmonary valve and artery. Patent ductus arteriosus.
19	1935	Manzini[58]	30	M	Fusiform aneurysm of right main branch.	Infection	Hypoplasia of aorta. Open foramen ovale. Marked dilatation of right ventricle. Dilatation trunk of pulmonary artery. Malignant endocarditis with vegetations of pulmonic and mitral valves.
20	1936	Botenga (I)[59]	62	M	Saccular aneurysm of trunk, 8 cm. in diameter.	Sclerosis	Enormous dilatation right ventricle. Widespread sclerosis pulmonary artery and branches.
21	1936	Botenga (II)[59]	24	F	Fusiform aneurysm of trunk, with narrowed sclerotic branches.	Congen. def.	Enormous dilatation right ventricle; left very small. Congenital sclerosis of pulmonary artery.
22	1937	Chiari (I)[34]	52	F	Ovoid aneurysm of right main branch.	Infection	Rheumatic endocarditis with button-hole mitral valve. Widespread thrombosis of pulmonary artery and of aneurysmal sac.
23	1937	Chiari (II)[34]	70	F	Spindle-shaped aneurysm of right main branch, size of a fist.	Syphilis; sclerosis	Endocarditis. Stenosis of pulmonary ostium.
24	1938	Gouley (I)[41]	50	M	Saccular aneurysm of right main branch.	Syphilis	Death from bronchopneumonia.
25	1938	Gouley (II)[41]	61	M	Saccular aneurysm of left main branch.	Syphilis	Chronic interstitial fibrosis of lungs. Pulmonary arteriosclerosis. Hypertrophy of right heart. Focal syphilitic lesions in aorta. Wassermann 4+. Death from bronchopneumonia.
26	1938	Gouley (III)[41]	70	M	Saccular aneurysm of right main branch.	Syphilis	Classical syphilitic aortitis. Hypertensive heart disease. Dilatation and hypertrophy of both ventricles.

TABLE II

TABULATION OF FINDINGS IN THIRTY CASES IN WHICH A DIAGNOSIS OF ANEURYSM OF THE PULMONARY ARTERY WAS MADE CLINICALLY

NO.	YEAR	AUTHOR	AGE	SEX	LOCATION AND TYPE	ETIOLOGY	ABNORMAL PHYSICAL FINDINGS IN THE CIRCULATORY SYSTEM AND REMARKS
1	1891	Aristoff[60]	21	M	Saccular aneurysm of trunk.	?	Thrill, pulsation and harsh systolic murmur second left interspace. Heart enlarged to rt.
2	1904	Rosenfeld[61]	--	--	Fusiform aneurysm of trunk.	--	
3	1912	Rak[62]	23	M	Aneurysm of trunk.	Congen. def.	Patent ductus arteriosus.
4	1918	Coleschi[63]	39	M	Fusiform aneurysm of trunk, extending into both branches.	Congen. def. Syphilis (?)	The case suggests simple diffuse dilatation without aneurysm.
5	1923	Conti[64]	43	F	Aneurysm of trunk.	Infection	Rheumatic carditis. Systolic thrill, pulsation, and bruit in second and third interspaces.
6	1924	Butler and Estapé[65]	21	M	Saccular aneurysm of trunk.	?	Emphysematous chest. Harsh systolic murmur in pulmonic area. Roentgenogram showed lengthening and lateral projection of conus shadow.
7	1921	Hormaeche[66]	--	M	Aneurysm of pulmonary artery.	Trauma	Followed fall from horse.
8	1924	Kranz[67]	43	M	Aneurysm of trunk.	Congen. def.	
9	1924	LeConte and Bordet[68]	54	M	Sacciform aneurysm of trunk.	Syphilis Sclerosis (?)	Pulmonary emphysema and chronic bronchitis. Pulmonic systolic hum.
10	1929	Balaban and Pokidoff[69]	41	M	Aneurysm of trunk extending into both branches.	Trauma (?) Syphilis (?)	Bulging third left costal arch, with systolic thrill, pulsation, and murmur.
11	1929	Horn[37]	23	F	Saccular aneurysm of left main branch.	Congen. def. Infection (?)	Rheumatic fever. Open ductus arteriosus.
12	1931	Lexow[70]	--	--	Aneurysm of trunk extending into left main branch.	Congen. def.	Dullness, bulging, systolic thrill, pulsation, and systolic murmur, third left interspace. Accentuation second pulmonic sound.
13	1931	Rodriqué and Battro[71]	27	F	Aneurysm of trunk.	Congen. def.	Open ductus arteriosus. Bulging, pulsation, and systolic murmur, third left interspace. Accentuation second pulmonic sound.
14	1931	Vogl[72]	52	F	Aneurysm of trunk.	Syphilis	Syphilitic arteritis of pulmonary artery.
15	1933	Calandre[73]	43	M	Aneurysm of trunk.	Syphilis	
16	1933	Guénard and Caubet[74]	44	F	Aneurysm of trunk.	Syphilis	Pulmonary syphilitic arteritis. Insufficiency of pulmonary valve. Pain third and fourth left intercostal spaces. Double pulmonic murmur.

17	1933	Nanu, Muscel et al.[75]	52	M	Saccular aneurysm of trunk.	Syphilis	Retrosternal pain. Question of aortic aneurysm with secondary pulmonary lesion.
18	1934	Borghetti[76]	35	F	Saccular aneurysm of trunk.	Infection	Rheumatic fever.
19	1934	Holst (II)[57]	43	M	Aneurysm of trunk extending into both branches.	Infection	Mitral stenosis of rheumatic origin, with secondary lung stasis. Strongly suggests simple dilatation.
20	1934	Holst (IV)[57]	54	M	Aneurysm of trunk.	Syphilis (?) Sclerosis (?)	Widened aorta. Calcified plaques roentgenographically.
21	1934	Holst (V)[57]	26	M	Aneurysm of trunk.	--	Dullness, systolic humming murmur, second left interspace.
22	1935	Gonzales[38]	39	F	Sacciform aneurysm of left branch.		Diagnosis made roentgenographically.
23	1935	Steiner[22]	37	M	Aneurysm of trunk extending into left branch.	Congen. def.	Infantilism. Pulmonary stenosis believed cause of aneurysm.
24	1936	Fowler[32]	59	M	Aneurysm of trunk.	?	Left upper thorax more prominent than the right. Visible impulse and loud, harsh murmur, second and third left interspaces. Death from rupture.
25	1936	Jennes (I)[1]	47	F	Aneurysmal dilatation of trunk and both branches.	Congen. def.	Findings suggest interventricular septal defect. Pulmonary regurgitation. Prominent upper left chest and widened dullness second interspace.
26	1936	Jennes (II)[1]	--	M	Aneurysmal dilatation trunk and both branches.	Congen. def.	Roentgenologic findings suggest widespread dilatation, entire tree of pulmonary artery. "Hilar dance."
27	1937	Roesler (VI)[28]	39	F	Saccular aneurysm left main lower branch 1.8 cm. in diameter.	Infection	Dilatation trunk and main branches of pulmonary artery. "Septic" endocarditis 18 years previously.
28	1937	Roesler (VIII)[28]	17	M	Saccular aneurysm of trunk.	Congen. def.	Right main branch pulmonary artery 2.1 cm. in diameter. Other congenital lesions.
29	1939	Boyd and McGavack (I)	42	M	Saccular aneurysm of left branch.	Syphilis	First symptom, profuse hemoptysis. Wassermann 4+. Presence of aneurysm confirmed at operation.
30	1939	Boyd and McGavack (II)	61	M	Saccular aneurysm trunk and left branch.	Syphilis Sclerosis (?)	Onset with chest pain. Wass. 4+. Cardiac conus enlarged, 2-3 interspaces. Prominent third rib. Systolic thrill and murmur in pulmonic area.

because of their low tonus; attention should also be directed to the fact that the pulse pressure in the lesser circulation exceeds the mean pulmonary arterial pressure.

Direct trauma rarely produces pulmonary artery aneurysm. One patient[16] had suffered a crushing injury, and, in two other cases,[17, 18] distortion of the artery by a contracting cicatrix resulting from gunshot wounds seemed responsible.

Congenital anomalies[19] were present in 66 per cent of the cases, and were deemed important etiologic factors in 43.2 per cent. Unequal division of the truncus arteriosus was evident in at least six, and open ductus arteriosus in twenty-four (23 per cent). Although pulmonary hypertension occurs in cases of patent ductus arteriosus and has been regarded as causative of aneurysm,[20, 21] patency of this passage is not uncommon without aneurysm. Accordingly, it seems reasonable to assume that some additional lesion, such as superimposed infection or atheromatosis, may contribute to the production of aneurysm in this group.[3, 7, 20] Pulmonary stenosis (thirteen cases) or insufficiency (two cases) may be present. In Steiner's case,[22] infantilism accompanied the cardiovascular anomalies. These lesions may be isolated or accompanied by pulmonary sclerosis. Patency of the interventricular septum increases intrapulmonic pressure and can cause arterial dilatation; it was present four times. Patency of the foramen ovale (eleven cases) was usually associated with more significant lesions (eight cases). Bicuspid and quadricuspid pulmonary valves, mitral stenosis, hypoplasia of the pulmonary artery, hypoplasia of the aorta (5.7 per cent), stenosis of the aorta (6.7 per cent), and aortic coarctation were also encountered.

Nonspecific arteriosclerosis of the pulmonary artery was present and regarded as partly provocative in 23 per cent of the cases.

Although Warthin[23] believed that syphilis was responsible in all of the fifty-one cases[7, 24] reviewed by him, this view has not remained unchallenged. Peck regarded only twenty-nine cases reported up to 1927 as possibly syphilitic in origin, and in only twelve of these did syphilis seem indisputably related;[25] however, Karsner[26] has questioned the role of syphilis in three of these twelve. Peck[25] also concluded that syphilis attacks the main trunk almost exclusively, and only occasionally extends to major branches. If this view is valid, it makes the old conception of the role of syphilis dubious; syphilis was supposed to affect the minute pulmonary vessels, to induce pulmonary hypertension, and, by concomitant, specific mesopulmonitis, to cause aneurysm. As a matter of fact, in only three of Peck's twenty-nine patients did the macroscopic and microscopic changes in the pulmonary artery aneurysm approximate those customarily seen in aortic aneurysm. However, if the assumption of D'Aunoy and von Haam is valid (twenty-three syphilitic aneurysms among eighty-seven cases), the additions reported since their

paper would raise that figure to thirty-three cases (31.7 per cent). The etiologic role of syphilis is difficult to understand, for the sex distribution is equal, and 88 per cent of the cases of aortic aneurysm, a lesion universally regarded as syphilitic in an overwhelming percentage of the cases, occur in males. Likewise, some doubt has been cast upon the older notion that pulmonary artery aneurysm in young individuals (usually in females) arises from a congenital malformation, and that in the older patients, who are predominantly males, it is caused by syphilis.

In eighteen patients infections other than syphilis seemed responsible; in seven, rheumatic endocarditis, in six, septic endocarditis, and in five, unspecified infection had been superimposed upon a congenital heart lesion.

Clinical Features.—For reconstruction of the clinical picture, twenty-eight cases in which the correct clinical diagnosis was reached have been added to the 111 cases in which the diagnosis was proved by necropsy. Oppenheimer's eight cases of idiopathic dilatation of the pulmonary artery were excluded because they represent congenital vascular anomalies of the artery, rather than aneurysm.[27] The cases of Roesler,[28] Laubry and Thomas,[29] and Taussig et al.,[30] are omitted for the same reason. On the other hand, although Jennes'[1] cases may well belong to the same group, they are included because it was inferred from clinical studies that an aneurysm was present. Likewise, the associated pathologic changes or complications may overshadow or mimic the signs in such a way as to preclude the correct diagnosis. Henschen[7] stated that only four of forty-six cases were "pure."

Some clarification of the clinical picture may be attained by the recognition of two groups of cases: (a) when the trunk is involved, exclusively or in combination; (b) when one or both main branches are affected. In the first form the complete picture of aneurysm of the pulmonary artery, described originally by Baader,[31] in 1765, may be seen. It is an aneurysm of signs *and* symptoms, whereas that of the branches is an aneurysm of symptoms. Syphilis was present in 29 per cent of the first group and 40 per cent of the second, while congenital lesions were equally distributed (43 per cent in each group).

The subjective symptoms in the two groups are similar. Palpitation has been considered the earliest symptom, but is not common (23.8 per cent). Dyspnea (76.9 per cent) and cyanosis (50.8 per cent) may appear early in cases in which there is an associated congenital malformation, while pain (60.5 per cent) and cough (78.8 per cent) antedate dyspnea and cyanosis in the absence of a congenital lesion. The dyspnea is often of the exertional type. A sensation of suffocation (4.8 per cent) or of "fullness" (40.3 per cent) in the chest is commonly ascribed to mechanical pressure. Precordial pain is not uncommon

(36.5 per cent), and is, at times, related to pericarditis. Shoulder pain with radiation down the arm (11.5 per cent),[32, 33] and distress in the back[34] and in various parts of the chest, associated with thromboses, have been reported. Substernal burning or pain (11.5 per cent) may or may not be due to an associated syphilitic aortitis. Cough (79.0 per cent) may be (a) nonproductive when caused by increased mediastinal pressure acting on the recurrent laryngeal nerve; (b) dry and subsequently productive, from bronchial irritation with or without bronchostenosis; and (c) productive of bloodstreaked sputum or frank hemorrhage resulting from pulmonary thromboses, often multiple. The first variety is uncommon, and recurrent laryngeal paralysis has not been reported.

Edema is always a late symptom; it is slight, recurrent, and usually limited to the lower extremities, although ascites is not uncommon. Save when syphilis affects a single branch of the artery, pulmonary stasis is constant.

The physical findings have not always been reported. The left side of the chest was more prominent than the right in forty-four of forty-eight cases. This enlargement was definitely localized to the region of the second and third costal cartilages in thirty-two cases, and is ascribed to the proclivity of aneurysm to affect the anterior wall of the vessel. Twice this development has occasioned detachment and necrosis of costal cartilages. A pulsation is observed more commonly in the second left intercostal space than elsewhere (64.5 per cent), and is usually attributed to an associated congenital defect. Fremitus in the same area may be either systolic (58.3 per cent) or diastolic (6.2 per cent). A diastolic thrill (12.5 per cent), with or without an associated murmur, usually signifies a complication, such as endocarditis. Dullness in the second left intercostal space (52 per cent) accompanies enlargement of the pulmonary conus and the trunk of the artery, which become applied to the chest wall as they enlarge. Right-sided cardiac enlargement is almost constantly present at autopsy, but it was commonly missed on physical examination (recognized in twelve of forty-eight cases). A systolic murmur may be most clearly audible in the second and third left intercostal spaces (83.3 per cent); usually it has a harsh, sawing, or rubbing character, but lacks a definite line of transmission.

The roentgenologic findings, which have been increasingly helpful in recognizing the lesion, may be summarized as follows:

A. Anterior view.—There is an accentuation of the middle arch, with increase in length and lateral projection. This may assume a globular form, and may pulsate if a thrombus has not formed. Extension to the right of the right heart border is seen in some cases. The left side of the silhouette moves in a "seesaw" manner, with the pulmonary conus

area and the ventricular shadow expanding alternately. In such instances the left border of the heart is formed by the right ventricle only; the left has been rotated dorsad.

B. Right anterior oblique view.—The aneurysmal shadow encroaches upon the retrosternal space, usually presenting a knoblike appearance in the posterior mediastinum below the level of the aortic arch and above the level of the left atrium. Such a picture is seen commonly in cases of dilatation of the right main branch, but a similar effect can occur when the aneurysmal pouch of the trunk develops to the right and in front of the aorta. Indentation of the esophagus below the normal aortic impression may result from direct pressure or transmitted pressure by way of the left bronchus.

C. Left anterior oblique view.—Encroachment upon the ventral and caudad aspects of the aortic window as a result of aneurysms of the trunk and of the left branch will be noticed; less frequently one sees a lesion of the right side.

Differential Diagnosis.—The diagnosis of aneurysm of the pulmonary artery seems justified when the following findings are simultaneously present: Pulmonary stasis, including dyspnea, cyanosis, oppression of the chest, and bloody sputum; prominence of the left side of the chest in the region of the second and third costal cartilages; a pulsation, a thrill, and a loud, superficial, sawing or rubbing systolic murmur in the second left intercostal space; hypertrophy and dilatation of the right side of the heart; a weak apex thrust, with dullness not going beyond the mammary line; lengthening and lateral projection of the pulmonary conus shadow, with the confirmatory roentgenologic signs previously mentioned. The electrocardiogram occasionally shows right axis deviation.

Among the conditions which may be confused with aneurysm of the pulmonary artery are aortic aneurysm, patency of the ductus arteriosus, idiopathic dilatation of the pulmonary artery, and various congenital heart lesions, especially interauricular septal defects. Roentgenologic examination usually distinguishes it from aortic aneurysm. Patency of the ductus arteriosus may be associated with pulmonary artery aneurysm, and a differentiation is impossible when thrombosis exists or when aneurysm of the patent ductus is present.[35] The unusually clear and sharply defined hilar pattern, with a comma-like appearance of the descending branch on the right, and the denseness of the large arteries, both in longitudinal views and cross section, are invaluable signs of idiopathic dilatation of the pulmonary artery. Although it may occur in other conditions,[28] the so-called "hilar dance"[36] is particularly prominent in cases of diffuse dilatation of the pulmonary tree. McGinn and White[78] found that an interauricular septal defect was of clinical significance in seven cases; it existed alone in one patient, and in association with patency of the ductus arteriosus in five persons with or with-

out other concomitant anomalies. While the roentgenologic findings in such cases may suggest aneurysm of the pulmonary artery,[78] the absence of murmurs, the right axis deviation, the late cyanosis, and "paradoxical embolism" are helpful in distinguishing the two lesions. The presence of bulging, the type of pulsation, and the thrill and murmur usually serve to differentiate aneurysm of the pulmonary artery from other congenital malformations except patency of the ductus arteriosus.

CASE REPORTS

CASE 1.—A Portuguese, 42 years old, on admission to the hospital July 27, 1937, stated that he had "brought up one quart of blood" ten days before. During the preceding three months his weight had decreased about twelve pounds. For six weeks he had suffered from a dry, hard cough and continuous, dull, occasionally knifelike pain in the back between the shoulder blades, usually referred to the left side, less frequently to the right or to the epigastrium, and aggravated by deepened respiratory movement. Following the hemoptysis he became markedly dyspneic, but this abated gradually during the several days prior to admission.

The patient's *past history* included chicken pox in childhood, "bilious fever" while in Africa in 1912, a middle-ear abscess in 1925, and "gassing" during the World War. He denied venereal infection. He had been married three years, and his wife had had no pregnancies. He had used a package of smoking tobacco daily for the preceding sixteen years and drank wine moderately.

Physical examination disclosed a well-proportioned, fairly well-nourished man, with no palpable enlargement of any of his lymph nodes. His chest was symmetrically developed, with bilaterally equal respiratory expansion. There was slight dullness to percussion posteriorly, extending outward from the root of the left lung. The breath sounds were normal. The heart was normal in size, shape, and position. The blood pressure was 95/60, the pulse rate, 88.

The patient has been continuously followed to date (September, 1939), either in hospital or clinic.

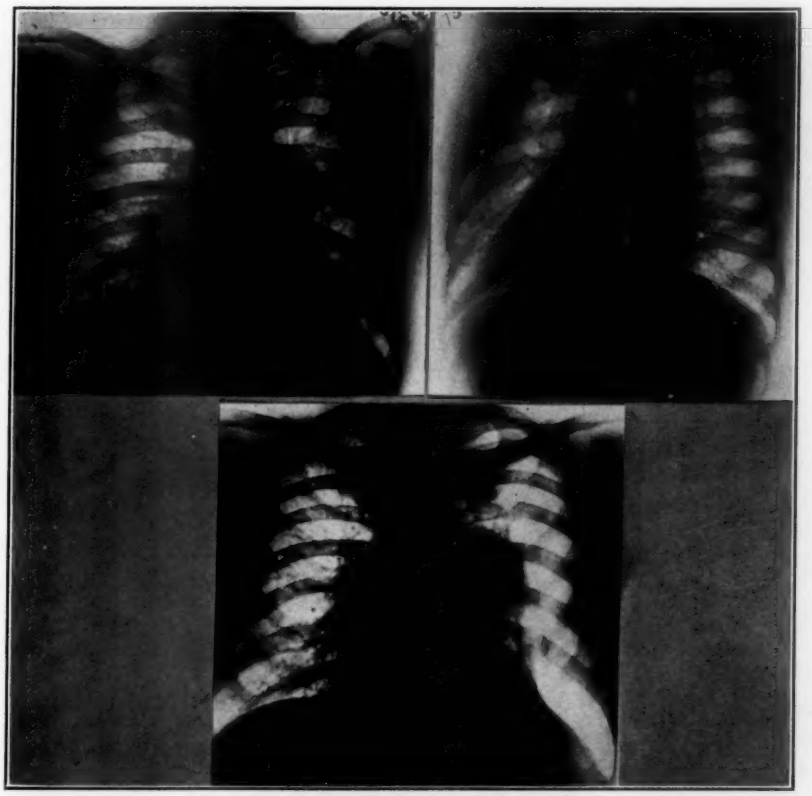
The blood count on several occasions has been always within normal limits. His blood Wassermann, Kahn, and Laughlin reactions have varied from strongly to moderately positive (4 plus to 2 plus) under antisyphilitic therapy. Urinalyses have been essentially negative. The sedimentation rate showed a 4 mm. drop in fifteen minutes, and a 40 mm. decrease at the end of one hour. His blood sugar, nonprotein nitrogen, and creatinine values, in mg. per cent, were 78.0, 31.5, and 1.7, respectively. His sputum has been repeatedly negative for tubercle bacilli. The fractional gastric analysis showed nothing abnormal.

Repeated bronchoscopic examinations revealed some edematous swelling of the aryepiglottic fold, and a smooth, indurated, pale red surface, with three small, circular depressions on the floor and medial wall of the left bronchus immediately below the bifurcation and pointing toward the mediastinum. The consistency of this wall was very firm and immobile. A piece of hard, cheeselike tissue was removed from this area. Histologic examination failed to show any evidence of malignancy or inflammatory change. The electrocardiogram showed no significant changes. There was no right axis deviation.

Frequent roentgenologic examinations (Fig. 1) of the chest in various positions demonstrated a sharply demarcated, nonpulsatile mass in the left hilar region. The periphery of the lung was normal in appearance. Thoracoscopy showed that the mediastinum was entirely free. The structures in the interlobar fissure and peripheral to the hilum were not visualized.

When all findings were considered, it was believed that the patient was suffering from a primary carcinoma in the hilum of the left lung which had not infiltrated peripherally to any appreciable degree. The case was therefore deemed ideal for lobectomy, and on Oct. 19, 1937, this operation was performed under tracheal anesthesia. In the region of the hilum there was a pulsating and expansile aneurysmal mass about the size of a small orange. This aneurysm seemed to extend into the lower lobe and protruded also towards the hilum and immediately posteriorly; it was

A. *B.*



C.

Fig. 1*A*, Case 1.—Anteroposterior view, showing very large shadow, extending from the left pulmonary conus, which had no expansile pulsation.

Fig. 1*B*, Case 1.—Right oblique view. Note the large aneurysmal shadow between the aortic arch and the left atrium.

Fig. 1*C*, Case 1.—Anteroposterior view following artificial pneumothorax, more sharply outlining the aneurysm of the trunk and left branch of the pulmonary artery.

completely frozen and adherent to the first part of the descending aorta. The attachments to the aorta were so intimate that no line of cleavage could be found. It was decided, therefore, not to attempt any type of surgical treatment of the aneurysm or its sac. The question whether it was an unusual form of aortic aneurysm was raised. At a later date, roentgenologic visualization of the heart and great vessel areas by the method of Robb and Steinberg[79] demonstrated conclusively that the aneurysm was located on the left main branch of the pulmonary artery.

Following thoracotomy the patient's course was relatively uneventful. The artificially produced pneumothorax disappeared within reasonable time, but the

patient's pain persisted to such an extent that paravertebral injections of alcohol, from the third to the ninth dorsal nerves, inclusive, were finally resorted to on Nov. 18, 1937, and repeated Nov. 30, 1937, in the region of the seventh and ninth roots.

His chest pain, still present on discharge from the hospital Dec. 1, 1937, did not entirely subside until late in February, 1938, since which time he has been reasonably asymptomatic. To date, Sept. 5, 1939, he has had the following antisyphilitic treatment: mercuric salicylate, one injection, 0.015 gm.; bismuth subsalicylate, 60 injections, 1 c.c. each; potassium iodide, 45 minims three times daily for three periods of approximately one month each, and sodium iodide intravenously, 2 gm. three times weekly for a period of two months.

The patient has shown gradual, constant improvement, and presents no complaints at the present time. Both his dry, harassing cough and his chest pain have completely disappeared. Roentgenograms show no appreciable change in the size of the shadow cast by the aneurysm. There are no cardiac changes secondary to the aneurysm.

COMMENT

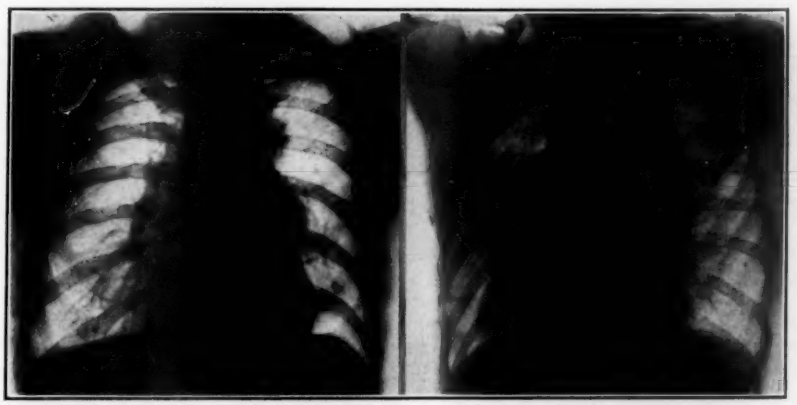
A lesion confined entirely to the left branch of the pulmonary artery with autopsy confirmation of the diagnosis has been observed in eleven cases. The diagnosis has been made clinically in two others.[37, 38] Operation for presumed tumor of the lung has been performed in one other case,[39] in which, however, the lesion involved the trunk as well as both branches of the artery. Hemoptysis as the first symptom of syphilis of the pulmonary artery has been stressed by Brenner[40] and by Laubry and Thomas,[29] who described two such cases. In these the symptoms were secondary to small multiple thrombi which, in turn, were ascribed to a diffuse syphilitic arteritis. Karsner[26] found thrombosis in seven of eleven cases of syphilis of the pulmonary artery. The long course which our patient has had, with the marked improvement under antisyphilitic medication, would suggest a smilar origin for his initial manifestation, hemoptysis. Our Case 1 proves to be an exception to Peck's[25] statement concerning the location of syphilis in the pulmonary artery. Moreover, there is reasonable proof that nine of the twenty-five aneurysms mentioned as affecting one of the main branches of the pulmonary artery were of syphilitic origin. The operative findings, the positive Wassermann, and the response to antisyphilitic therapy leave little doubt as to the character of the saccular lesion in the foregoing case.

CASE 2.—A 61-year-old white man, nine months before admission to the hospital on June 1, 1938, noticed severe pain in the upper left chest, with radiation to the angle of the scapula on that side. He gave no history of immediately preceding strain or infection and had been able to pursue his occupation as a painter until the onset of the pain.

His *past history* was essentially negative; in particular, there was nothing which might suggest either congenital or acquired heart disease.

Physical examination revealed a well-developed and well-nourished man who had marked hardening of all visible and palpable peripheral arteries. His area of cardiac

dullness was enlarged in the second and third intercostal spaces to the left. Definite prominence of the left third rib and of the second and third intercostal spaces, with marked pulsation in the latter, was noted. A marked systolic thrill was felt in this area, and a loud, harsh, but low-pitched, systolic murmur could be heard. The blood pressure was approximately 130/75 in both arms, and the heart rate was 92. The blood Wassermann was strongly positive (4 plus). His electrocardiogram revealed right axis deviation. The main deflection was slurred in all leads except Lead II. T was very low in Lead I, very high in Lead III, and inverted in Lead IV. The teleroentgenogram (Fig. 2) showed a dilated conus arteriosus, with a semilunar shadow the size of a peach or small apple superimposed upon it and extending into the left lung field. The aorta could be distinctly separated from this shadow throughout its entire course. There were calcified plaques along the right border and over the pulmonic curve of the heart.



A. *B.*

Fig. 2*A*, Case 2.—Anteroposterior view, showing the rounded shadow extending out from an already prominent pulmonary conus.

Fig. 2*B*, Case 2.—Right oblique view, showing aneurysmal dilatation of the pulmonary conus and extension of the aneurysm along the left pulmonary branch.

COMMENT

In view of the positive Wassermann, the absence of preceding heart disease, and the apparent rapidity with which the lesion developed, syphilis would appear to be the most likely etiologic factor in this case. While the patient's age was above the average, it must be remembered that Gouley[41] has seen three cases, in which syphilis was proved to be the cause of the aneurysm, occurring in individuals between the ages of 59 and 70. The oldest autopsied patient whose lesions were considered to be syphilitic was a woman 75 years of age.[42] In six of thirty-three reported cases of syphilitic aneurysm in which an autopsy was performed the patients were over 60 years of age. An underlying congenital defect seems unlikely in the present instance, although Weischer[12] found patency of the ductus arteriosus and congenital aortic stenosis in a woman, 62 years old, who had previously shown no evidence of congenital heart disease. The calcified plaques demonstrated roentgenologically in Case 2 could have occurred as a secondary result of either syphilis or pure arteriosclerosis.

The age, mode of onset, clinical course, and physical and roentgenologic findings were in sharp contrast to those in Case 1. The mode of onset resembled that seen by Fowler,[32] and, as in his case, there was no previous history of heart disease.

In the two cases described in the present report, the aneurysms were similar only in that apparently they were both of spirochetal origin. Otherwise, on the one hand we have an aneurysm of symptoms with the lesion completely localized to a branch of the artery, and, on the other, involvement of the trunk of the vessel with its accompanying diagnostic group of symptoms and physical signs.

SUMMARY

1. A statistical survey has been made of the clinical and pathologic features of 111 cases of aneurysm of the pulmonary artery in which the diagnosis was confirmed by autopsy.

2. Some of the features of thirty cases in which a clinical diagnosis of aneurysm of the pulmonary artery was made have been summarized.

3. Two cases of aneurysm of the pulmonary artery are reported.

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CARDIAC METASTASIS FROM MALIGNANT MELANOMA

Report of Four Cases

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METASTATIC tumors of the heart are rare. Nicholls[1] tabulated the figures given by a number of authors and found that of a total of 36,980 autopsy cases of carcinoma there were metastases to the heart in 109, or 0.29 per cent. Scott and Garvin[2] report that in a series of 11,100 consecutive autopsies performed at the Cleveland City Hospital there were 1,082 cases of malignant disease; the heart, including the pericardium, was involved by metastatic tumor in 118 cases, an incidence of 10.9 per cent. Among these cases there were ten malignant melanomas, five of which metastasized to the heart. Lymburner[3] states that from 1915 to 1931, in a series of 8,550 autopsies at the Mayo Clinic, there were thirty-six secondary carcinomas and sixteen secondary sarcomas of the heart; six of the tumors were pigmented. Stout,[4] in his book on cancer, states that at the Presbyterian Hospital of New York one primary and fifteen secondary tumors of the heart were found in a series of 1,171 autopsies over a period of ten years; no mention is made of melanotic tumors. Chayka,[5] in 1937, reported five cases of cardiac metastasis, none of which was melanoma.

A complete review of the literature reveals reports of only twenty-three cases of malignant melanoma with cardiac metastasis. Here we present four additional cases of cardiac metastasis from malignant melanoma which were observed in the Saint Louis University group of hospitals.

Case 1.—Mrs. M. V., 30 years of age, had had a pigmented nevus removed from the posterior aspect of the right calf seven months earlier. On physical examination the lungs and heart were negative. A scarred area was found on the posterior surface of the right calf, with small, pigmented nevi surrounding it. In the right femoral region there was a hard mass, 5 cm. in diameter, which was slightly tender, reddened, could not be reduced, and was fixed to the surrounding tissues. Enlarged lymph nodes were palpable around the mass. Biopsy revealed that the tumor was a melanocarcinoma.

At autopsy the body was found to be well developed, but showed some evidence of recent emaciation. Nothing remarkable was noted on examination of the head, neck, chest, and abdomen. In the right calf, near the popliteal fossa, there was a scarred area, the site of a previous cauterization of a pigmented mole. The pericardial cavity was normal in size and contained about 20 c.c. of straw-colored fluid; the serosa lining it was smooth and glistening throughout. The exterior of the pericardium was studded with small white nodules ranging from the size of a pinhead to that of a dime. The heart was about three-fourths the normal size, and its

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musculature was rather flabby. The epicardial surface was smooth and glistening. The left ventricle was slightly enlarged. In the endocardium of the left ventricle there was a small grayish mass about 4 mm. in diameter. There was nothing remarkable about the aortic, tricuspid, or pulmonary valves. The edges of the mitral valve were only moderately thickened.

On microscopic examination, the heart muscle was found to be the seat of advanced albuminous degeneration with moderate fragmentation and segmentation of the fibers and some interstitial scarring. Just underneath the endocardium there was a metastatic nodule of carcinoma cells of the pigmented type, most of which were polyhedral and contained a small amount of pigment (Fig. 1).

The anatomic diagnosis was malignant melanoma of the skin of the right popliteal fossa, with metastases to heart, lungs, liver, kidneys, and inguinal and iliac lymph nodes.

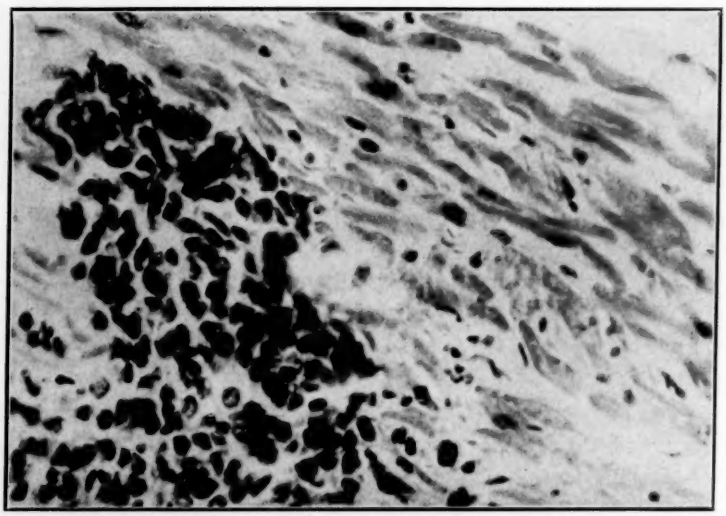

Fig. 1, Case 1.—The tumor cells are polyhedral and contain a small amount of pigment.

CASE 2.—Mrs. S. L. A. was 69 years of age. About five months earlier she had had a melanotic whitlow on the right thumb, which was incised. A short time after the incision the finger became painful, and a tumor appeared and rapidly increased in size. The mass was incised again, and, after roentgen therapy, it had been decided, two and a half months before admission, to amputate the right thumb. Since that time the patient had had marked weakness and loss of appetite, together with pain or discomfort throughout the body resulting from numerous small nodules which appeared in the skin. Examination of the lungs disclosed decreased intensity of the breath sounds in the right upper lobe. Examination of the heart showed nothing abnormal. A mass measuring about four by six inches was palpable in the epigastrium. There were numerous subcutaneous nodules over the back and abdomen, and especially in the axillae.

At autopsy the body was cachectic. Throughout the skin there were many nodules of various sizes and shapes, rounded, and raised above the surface, with a dark bluish or purplish discoloration. These nodules were most numerous about the chest, shoulders, and abdomen. They were less prominent on the extremities, but some could be found even in the scalp. In the mandible in the region of the right canine tooth, which was missing, there was a medium-sized tumor nodule of soft consistency and

a bluish color. The pericardial cavity contained about 4 c.c. of a thin, clear, yellowish fluid. The heart was of average size; its epicardial surface was studded with dark nodules of various sizes, resembling those on the skin. The coronary arteries were slightly tortuous and thickened with fibrous tissue. All of the valve leaflets were thin and filmy. The myocardium was riddled with numerous nodules of the same kind as those mentioned above.

On microscopic examination, the muscle fibers were pale, granular, and degenerated. Spread in between the muscle fibers there were numerous clusters of metastatic tumor cells, most of which were necrotic and degenerated. Many of these tumor cells contained considerable quantities of a golden-brown pigment. Most of the cells were spindle-shaped and did not show any particular arrangement; they had invaded the myocardium extensively (Fig. 2).

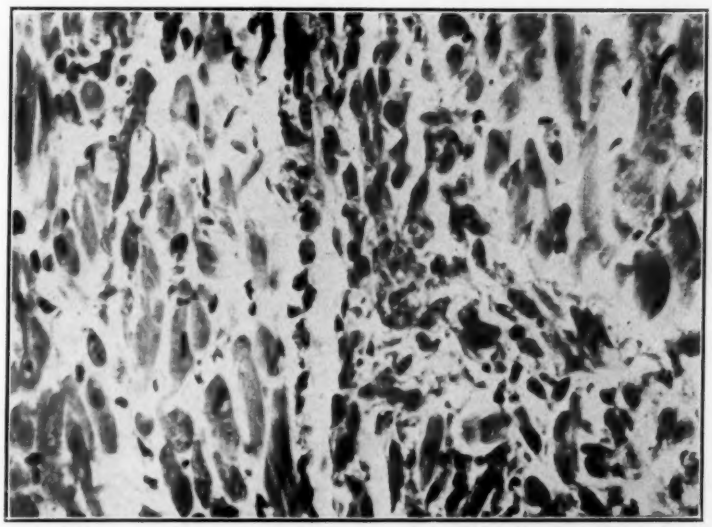

Fig. 2, Case 2.—The tumor cells are mainly spindle-shaped and contain much pigment.

The anatomic diagnosis was malignant melanoma of the right thumb (subungual), with metastases to heart, lung, aorta, liver, intestine, pancreas, kidney, and adrenal.

CASE 3.—Mr. J. Q., a white man, forty-four years of age, had begun to notice numbness and paresthesia on the left side of the body and in upper legs and arms about seven or eight months previously. He had had severe cramps in the calves of both legs. Three weeks before admission he began having headaches (frontal and occipital) which increased in severity and were accompanied by nausea and vomiting. His vision was poor, and he had diplopia. At rest, the right palpebral fissure was narrower than the left. Ophthalmoscopic examination showed blurring of the disc margins, with papilledema, and congestion of the veins of the fundus of the right eye. The fundus of the left eye was normal. The neck and chest were normal. The abdomen was tender to pressure, and there was muscular rigidity in the right upper quadrant and right flank. There were no palpable masses. Neurological examination showed that the patient was confused and disoriented. Examination of cranial nerves 1, 3, 4, 5, 6, 8, 9, 10, 11, and 12 showed nothing abnormal. Vision in right eye (O.D.V.) was reduced to 20/40; vision in the left eye (O.S.V.) was normal, 20/15. There was weakness of the lower facial muscles on the right side. Although the patient was right handed, his gripping power was less on the right than on the left.

The finger-to-nose test showed that there was proximal afferent ataxia in the right arm. The abdominal reflexes were active and equal. The patellar reflexes were equal and normal. The heel-to-toe test showed that sense of position was unimpaired in the lower extremities. The urine was clear, acid in reaction, and contained neither albumin nor sugar. The erythrocyte count was 4,630,000, the hemoglobin 12.5 gm., and the leucocyte count 9,200. The blood Wassermann and Kahn reactions were negative. The nonprotein nitrogen content of the blood was 30 mg. per cent, and the blood sugar value 96 mg. per cent. The spinal fluid was clear, but contained 70 lymphocytes per c. mm.; the Queckenstedt test was positive. The patient was operated on for brain tumor. The immediate postoperative condition was fair, but the day before death his condition changed for the worse.

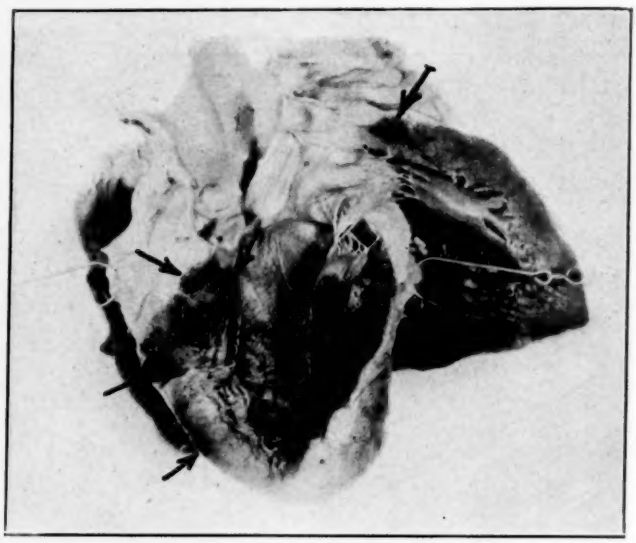

Fig. 3, Case 3.—The arrows point to metastatic nodules of melanoma in the myocardium.

At autopsy the body was that of a well-developed, poorly nourished white man who appeared older than he really was. Rigor mortis had set in. Hypostatic congestion was present. There was edema of the entire scalp. Two recent wounds were found in the right occipital region. The left sclera and conjunctiva showed evidence of hemorrhage; the right were normal. The pupils were slightly dilated, and equal. The neck, chest, and abdomen were negative. The pericardial cavity contained about 5 c.c. of a greenish-yellow fluid. The heart was of normal size, but the walls were slightly thinned. There were four small, black, flat, smooth tumor growths, about ½ cm. in diameter, in the myocardium of the left ventricle. There was slight thickening of the wall of the aorta. The coronary vessels were normal. The valve leaflets were thin, filmy, and intact. The epicardium was normal throughout. In the mediastinum there were several small tumor nodules, the largest of which measured 3½ to 4 cm. in diameter. The brain contained a large number of round, black, metastatic nodules which varied from ½ to about 4 cm. in diameter. The largest nodule, about 4 to 5 cm. in diameter, was present in the right temporo-occipital region.

Microscopic examination of sections taken from the heart muscle showed a marked degree of edema and congestion throughout, some increase in segmentation and fragmentation of the muscle fibers, and a moderate degree of brown atrophy of the myocardium. In the section there was a large, metastatic nodule formed by large, epithelial-like cells which were polyhedral and contained much brown pigment inside

the cytoplasm (Fig. 4). This pigment proved to be melanin, and the nodule was a metastatic melanoma. Different sections taken from the brain showed multiple metastatic nodules of melanoma, consisting of large, epithelial-like, hyperchromatic cells laden with brown pigment which did not give the Prussian blue reaction. Most of the cells were atypical, grew irregularly, and showed many mitotic figures.

The anatomic diagnosis was malignant melanoma, with metastases to lungs, heart, brain, liver, stomach, both kidneys, bladder, and omentum; the primary growth was most probably in the medulla of the left adrenal.

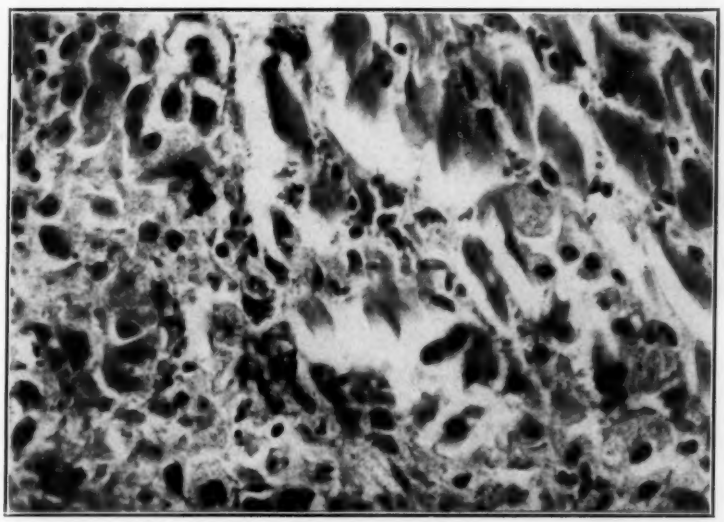

Fig. 4, Case 3.—The tumor cells are for the most part polyhedral and contain much pigment.

CASE 4.—Mrs. S. S. was a colored woman, 39 years of age, who walked into the hospital on June 25, 1938. She complained of severe pain in the left side of the head of two years' duration. She also complained of numerous tender and enlarged lymph nodes which were distributed over the entire body. The patient had had a small tumorlike mass removed from the left parietal region about one year before. The operative wound had been slow to heal. She had received roentgen therapy. Examination revealed a well-developed and well-nourished woman, lying in bed in some distress. On the left side of the head there was an old operative scar, the result of the extirpation of the tumor mass mentioned above. There was increased intraocular tension in both eyes, and at times the sight was impaired. The pupils reacted slowly to light and in accommodation. There were several large, firm lymph nodes in the anterior cervical region; similar masses were also present in the chest. A loud systolic murmur was heard at the mitral and pulmonary areas. The abdomen was normal in contour; several enlarged lymph nodes were felt and seen over this area, and especially in both inguinal regions. An enlarged lymph node was present in the popliteal fossa on the right side. Biopsy revealed that the tumor was a melanosarcoma. The blood pressure was 130/70; the blood Wassermann and Kahn reactions were negative; the erythrocyte count was 3,990,000; the hemoglobin 75 per cent; the leucocyte count 5,350. The urine was clear, acid in reaction, yellow, and the specific gravity was 1.020; it contained slight traces of albumin, but no sugar. There were occasional erythrocytes and leucocytes in the urine. The patient was readmitted to the hospital on Sept. 13, 1938, complaining of abdominal disten-

tion and multiple growths on the abdomen and neck. A paracentesis was performed, and about 1,600 c.c. of reddish ascitic fluid removed. The patient grew steadily worse.

At autopsy the body was emaciated. There was a small scar in the left parietal region, and the hair was missing in this area. A few small, dark nodules were seen on the left upper eyelid. The nose and ears were normal. There were some other black nodules on the face. Examination of the neck revealed many rounded masses of a dark purplish color on both sides, but mainly on the left. These were large lymph nodes. There were also palpable masses in both supraclavicular regions and both axillae. There were many dark nodules of different sizes scattered throughout the chest wall, the abdominal wall, and lower extremities. There was a large, black, metastatic nodule at the margins of the anus, and another on the right buttock. The pericardial cavity was completely obliterated by fibrous adhesions, and somewhat decreased in size because of the small size of the heart itself. On the epicardium there were several small, black, round nodules, and a large calcified plaque on the

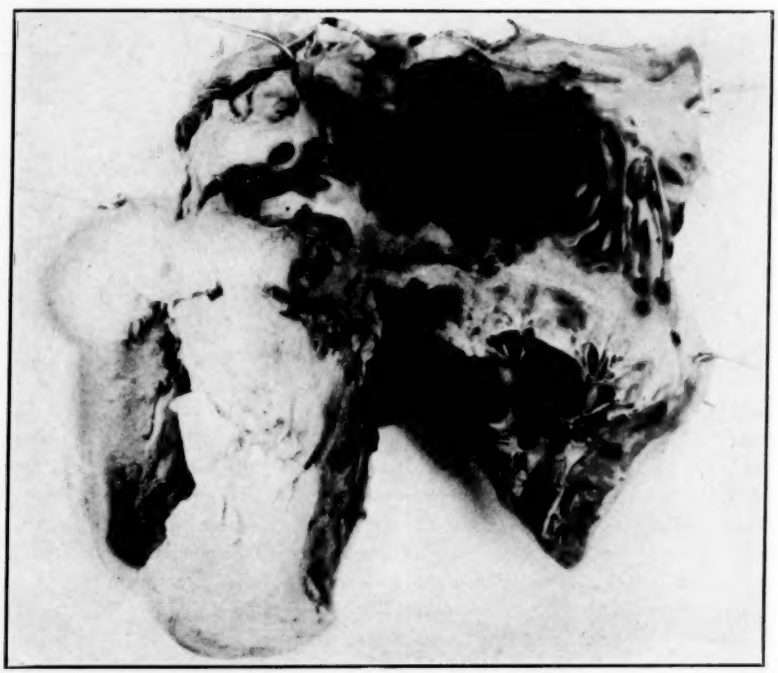

Fig. 5, Case 4.—Multiple metastatic nodules of melanoma in the right atrium and right ventricle.

left ventricle posteriorly. In opening the heart in the usual way, we could see large, black, metastatic masses in the right atrium. In cutting through the tricuspid valve we found numerous metastatic nodules, quite black, in the right ventricle, and there was a fairly large mass of this same black tumor underneath the leaflets of the tricuspid valve affecting the myocardium of the right ventricle (Fig. 5). There was a large pedunculated tumor attached in the region of the conus arteriosus, growing into and almost completely plugging the pulmonary orifice (Figs. 6 and 7). In opening the left atrium and left ventricle we could see some metastatic nodules of melanoma. The myocardium itself showed some small, black nodules spread throughout, between the muscle fibers. The consistency of the muscle was somewhat soft and atonic.

No gross pathologic findings were seen on the heart valves themselves. The aorta showed a moderate degree of atherosclerosis. There was a large, rounded tumor in the lower lobe of the right lung. On section, this mass was black and soft. On the wall of the stomach there were several black tumor nodules; the largest, measuring about 2 cm. in diameter, had ulcerated the gastric mucosa. Throughout the small and large intestine, omentum, and mesentery there were multiple black tumor nodules. In the pelvis, and progressing toward the right lower quadrant, there was a very large black tumor measuring about 10 by 15 cm.; this mass was located on

Fig. 6, Case 4.—Large pedunculated tumors in the right ventricle, in the region of the conus arteriosus.

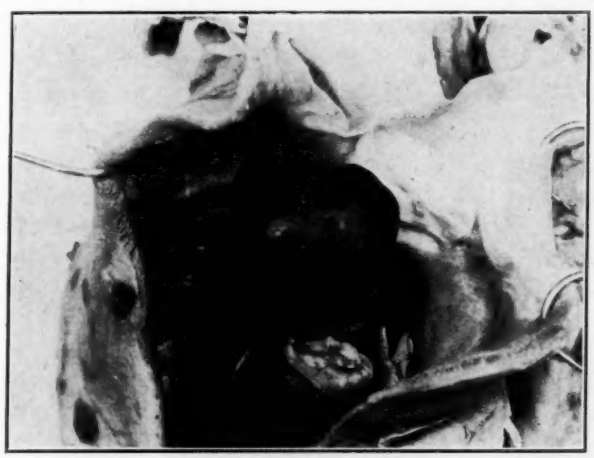

Fig. 7, Case 4.—Large tumor causing almost complete occlusion of the pulmonary orifice (the patient had a loud systolic murmur in the pulmonary area).

the right side of the pelvis in the region of the right ovary, which could not be found. Several metastatic nodules were found in the liver, pancreas, right kidney, and bladder.

On microscopic examination, the sections of the heart showed a marked congestion throughout. There was also increased fragmentation and segmentation of the muscle fibers, and brown atrophy of the myocardium. Spread throughout the section there were two or three metastatic nodules formed by large, hyperchromatic, atypical cells, most of which were spindle-shaped, and laden with large amounts of granules of a dark brown pigment (Fig. 8). The pigment was melanin, and the cells were those of metastatic nodules of malignant melanoma. The coronary vessels were not particularly thick.

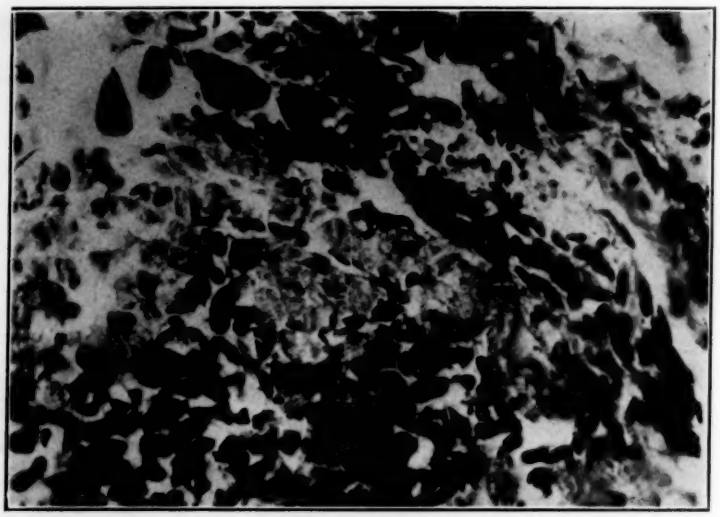

Fig. 8, Case 4.—Most of the tumor cells are spindle-shaped and contain much pigment.

The anatomic diagnosis was malignant melanoma, primary in the scalp, with multiple nodules in the skin and lymph nodes; large metastases to the heart; metastasis to lungs, liver, stomach, pancreas, intestine, and abdominal wall.

COMMENT

We feel strongly that malignant melanoma is one of the tumors which show a relatively common tendency to invade the heart. In Scott and Garvin's series of cases there were ten melanomas, five of which metastasized to the heart (50 per cent); in our autopsy records there were seven cases, in four of which cardiac metastases occurred (57 per cent). The cases found in the literature are the following: In 1903, Delhern and Laignel-Levastine[6] reported a case of melanotic sarcoma with metastasis in the heart. Goldstein[7] mentions that Prudhomme, in 1867, reported a case of malignant melanoma with cardiac metastasis in a man; that Erkes, in 1910, reported a diffuse melanosarcoma of the heart; and that Napp refers to two cases of melanosarcoma of the heart described by Deguy. Goldstein also reports three cases of his own. One was that of a melanotic sarcoma which probably started in the right

eye; in the second case there was also a melanotic sarcoma with marked involvement of the adrenals and retroperitoneal and mesenteric lymph nodes; in the third case the tumor originated in a pigmented, soft mole of the labium majus. Lisa,[8] in 1923, reported the case of a man, 42 years of age, who had a black mole on the upper jaw; it started growing fast, in spite of radium treatment, and soon involved the cervical lymph nodes; numerous subcutaneous masses also developed over the entire body. The autopsy revealed metastasis to heart, lungs, trachea, liver, spleen, kidney, pancreas, stomach, large and small intestine, omentum, and ribs. Yater,[9] in 1931, described a case of melanosarcoma of the left eye in a man 64 years of age; there were metastases to the brain, heart, lungs, omentum, colon, and pancreas. Burke,[10] in 1934, reported two cases. The first was that of a white woman, 56 years of age, who, a year and a half before death, had a pigmented mole removed from the right wrist by fulguration, followed by roentgen therapy. The lymph nodes in the right axilla and right supraclavicular region became involved soon afterward. The autopsy revealed malignant melanoma, with metastasis to heart, ribs, adrenal, spleen, liver, lungs, kidney, and axillary, mediastinal, and retroperitoneal lymph nodes. Burke's second case was that of a 46-year-old man who had a black wart removed from his back nine months before death. All of the lymph nodes soon became involved, and the autopsy revealed a malignant melanoma which had metastasized to heart, omentum, pancreas, lungs, liver, and adrenals. Lymburner says that in 8,550 autopsies at the Mayo Clinic, from 1915 to 1931, there were six cases of malignant melanoma with cardiac metastasis; in four of the cases the tumor was primary in the skin, and in two, in the eye. In Scott and Garvin's[2] series of 11,100 consecutive autopsies at the Cleveland City Hospital, there were five cases of malignant melanoma with metastasis to the heart. Among 3,600 autopsies performed in the Saint Louis University hospitals, there were seven cases of malignant melanoma, in four of which cardiac metastasis had occurred.

In most of the cases the involvement of the heart was not suspected clinically. In one of the cases reported by Scott and Garvin, the patient had attacks of paroxysmal auricular fibrillation, and the possibility of cardiac metastasis was considered. In only one of our cases were there any signs that the heart was involved; in this case there was a loud systolic murmur in the pulmonary area caused by a large tumor mass which almost completely occluded the pulmonary orifice. In most of the reported cases the patients were white; melanomas in the negro are very rare. Bauer,[11] in 1926, in a review of the literature, could find only fourteen reported cases of malignant melanomas in negroes; he did not include melanotic orbital tumors. One of our cases was in a negress; the cardiac metastases in this case were larger than in the other three cases reported here.

SUMMARY

1. Four cases of cardiac metastasis from malignant melanoma are reported.

2. A review of the literature discloses only twenty-three such cases. Doubtless others have been reported, but under the heading of carcinoma or sarcoma.

3. We believe that cardiac metastasis in cases of malignant melanoma is more frequent than the paucity of reported cases would lead one to think.

4. In one of our cases the patient was a negress, and this is the first time such an occurrence has been reported in that race.

5. In none of the cases presented here was the involvement of the heart suspected clinically.

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Department of Clinical Reports

ARTERIOVENOUS FISTULA OF THE LUNG ASSOCIATED WITH POLYCYTHEMIA VERA: REPORT OF A CASE IN WHICH THE DIAGNOSIS WAS MADE CLINICALLY

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SEARCH of the available literature has failed to disclose a case of arteriovenous fistula of the lung in which the diagnosis was made clinically.

REPORT OF A CASE

A man, 40 years of age when first observed at the Mayo Clinic in 1932, related that he had been a "blue baby," small and frail at birth. He continued to be small and underweight until he reached the age of 9 years, when he began to grow rapidly. Through boyhood he played actively and enjoyed apparently good health.

The patient entered the United States Army in 1916, at the age of 24 years. The medical officer who examined him on his enlistment was the first physician to call his attention to the fact that he was cyanotic and that his fingers were clubbed. No abnormal condition of his heart was found at that time. In 1917 he had severe influenza and pneumonia but recovered completely. Thereafter he enjoyed moderately good health until 1924, when, at a time of considerable stress, he suddenly became generally tense, then weak, and finally dropped to the floor. This attack, in which he did not lose consciousness, lasted about thirty minutes. He never had another similar attack.

For a few years before the patient first came to the clinic he had had attacks characterized by invisible tremor of the body, a sensation of fullness in the head, transient tinnitus and vertigo, and tension in the muscles of the back of the neck. Diplopia occurred in one of these attacks. He also had noticed numbness, without tingling, of the hands and feet, slight dyspnea on exertion, and distress in the precordium. During the attacks, he reported, his pulse rate occasionally increased from a normal of 60 to 130 per minute. His systolic blood pressure varied between 90 and 100 mm. of mercury. In the eight years before we first saw him, examination of his blood had disclosed 5,000,000 to 6,000,000 erythrocytes per c.mm. He related that his skin always had been dark.

When the man first was examined at the clinic he weighed 116 pounds (53 kg.) and was short and asthenic. His skin, lips, nail beds, and mucous membranes were cyanotic, and clubbing of his fingers and toes was noteworthy. The blood pressure was 88/52. The pulse rate was 56, and the temperature, 98.4° F. Urinalysis gave negative results. The blood, which was of increased volume, contained 20.6 gm. of hemoglobin per 100 c.c.; the erythrocytes varied from 5,440,000 to 6,220,000 per c.mm., and the leucocytes numbered 3,200 per c.mm. The spleen was not palpable.

The diagnosis was atypical polycythemia vera, treatment for which consisted of venesection, followed by administration of phenylhydrazine. It was believed that

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the polycythemia had developed following the influenza and pneumonia fifteen years before, at which time also there may have been a pulmonary abscess.

The patient returned to the clinic in April, 1938. Since his previous visit he had undergone varied treatment. Numerous venesections had afforded him temporary relief. After a course of these, a small capsule of phenylhydrazine had been given to him twice a day. He had taken benzol for a month, but this had had little or no effect. In the latter part of 1935 he had noticed a "hot spot" in his left shoulder. Consciousness of this had been followed by a sense of constriction in the thorax, and, within four hours, he had scarcely been able to breathe. Consequently, he had been taken to a hospital, and oxygen had been administered. He remembered little of the next two weeks but had had considerable pain. Gradually he recovered from this attack. In December, 1936, because of weakness and shortness of breath, he had entered a Chicago hospital, where a small capsule of phenylhydrazine

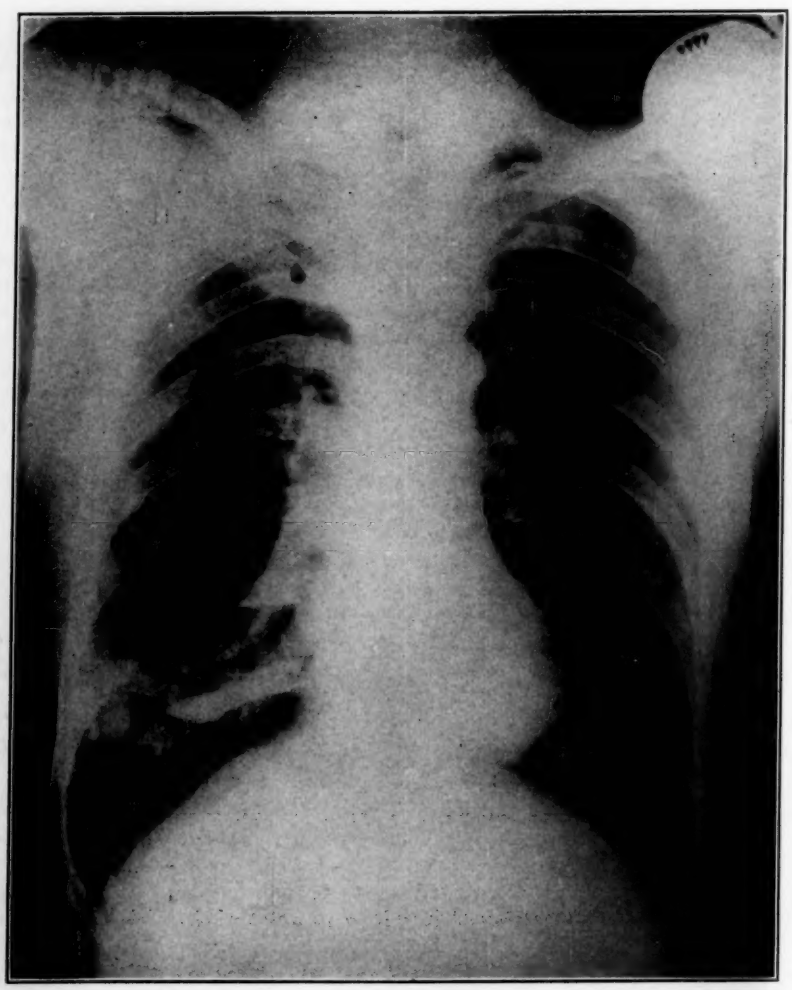

Fig. 1.—Roentgenogram of the thorax revealing what appears to be bronchiectasis in the lower right portion of the thorax. This represents the region in which two dilated vessels, originating in the right hilum, appeared to communicate in the parenchyma of the lung. An arteriovenous bruit was audible over this region.

had been administered daily. He remained there nine months. Thereafter, and until a month before his second visit to the clinic, he had taken 4 minims (0.25 c.c.) of solution of potassium arsenite (Fowler's solution) three times a day.

At the time of this second admission the patient appeared undernourished. Clubbing of the fingers and toes and cyanosis were about the same as before. The peripheral veins were dilated, especially those of the right anterior portion of the thorax and those of the legs; the latter were rather conspicuously varicose. A continuous, blowing murmur, or bruit, was heard over the right posterolateral aspect of the thorax, in the region of the eighth and ninth ribs. This murmur had not been heard when the patient was examined at the clinic in 1932, but he said that it had been heard by an army medical officer in 1916. The edge of the liver was palpable 5 cm. below the right costal margin. The blood pressure (94/60) was scarcely higher than it had been at the previous admission, and the temperature remained normal. The pulse rate, however, which had been slow in 1932, was 74. The retinal arteries and veins were dilated and appeared cyanotic, and the margins of the optic disks were slightly blurred. A number of punctate patches characteristic of old, chronic choroiditis were present.

The urine contained a few erythrocytes and pus cells. The value for hemoglobin was 23.7 gm. per 100 c.c. The erythrocytes numbered 6,470,000, the leucocytes, 7,300, and the platelets, 104,000. The hematocrit reading was 66 per cent on one day, and 71 per cent four days later. The total plasma volume was 1760 c.c., or 35 c.c. per kg. of body weight, and the whole blood volume was 6068 c.c., or 121 c.c. per kg. (normal, 85 c.c. per kg.). The electrocardiogram revealed a rate of 67, sinus bradycardia, slurred QRS complexes in Leads II and III, inverted T waves in Lead III, and positive T waves in the standard fourth lead. Roentgenoscopic examination gave evidence that the heart and mediastinum were normal, except for small patches of calcification in the anterior portion of the pericardium. There was infiltration of the posterior portion of the base of the right lung which was thought to be the result of bronchiectasis, as no pulsation was noted. However, the history did not suggest chronic bronchiectasis. Bronchoscopic examination, moreover, was deemed inadvisable.

An attempt was made to visualize a vascular lesion in the right side of the thorax. A radiopaque medium was injected into the basilic vein; then a series of roentgenograms was made. These revealed two dilated vessels arising in the right hilum, and communicating in the parenchyma of the right lung in the region of the ninth and tenth ribs posteriorly (Fig. 1). This region corresponded with that where the bruit was audible.

The probable diagnosis was now arteriovenous fistula of the right lung. Treatment consisted of venesection at frequent intervals, to keep the blood volume within normal range.

COMMENT

From an anatomic standpoint, the lesion in the right lung could properly be classified as an hemangioma, but physiologically it represented an arteriovenous fistula, and we felt that the increased blood volume was a result of such a fistula. That increase in blood volume is invariable in the presence of large arteriovenous fistulas is well known. Cardiac dilatation and hypertrophy also would be expected; their absence in this case perhaps was due to the fact that the arteriovenous fistula involved only the pulmonary circulation.

Hemangiomas usually are described as irregular, intercommunicating blood spaces surrounded by fibrillary connective tissue and smooth

muscle. They are divided into the simple, or capillary, nevus, the cavernous nevus, and the plexiform nevus. Hemangiomas vary greatly in size and shape; some are recognizable only with the aid of the microscope, while others weigh several pounds. Virchow long ago demonstrated that the intercommunicating blood spaces in hemangiomas really represent abnormal arteriovenous communications. In the so-called cavernous and plexiform types, bruits are often present. Many additional descriptive terms, such as "pulsating venous aneurysm," "angioma arteriole," and "arteriovenous varix," have been used to describe the superficial manifestations of a pathologic process which we prefer to call "arteriovenous fistula." Irrespective of size and shape, and notwithstanding the presence of a bruit, all hemangiomas represent abnormal arteriovenous communications between arteries and veins, by means of which arterial blood flows from arteries to veins without passing through the normal capillary bed. Reid[1] and one of us (Horton[2]) have held this view for a number of years.

Bowers,[3] in 1936, reported the case of a child who died suddenly, on the second day after birth, from a fatal pulmonary hemorrhage. The source of the hemorrhage was found to be an hemangioma of the lung. Rodes[4] also reported a case in which a man, 25 years of age, died suddenly from pulmonary hemorrhage; it was found that an hemangioma of the lung had ruptured. No mention of a bruit over the thorax was made in reports of these cases. The diagnosis in each instance was made at necropsy. We have no doubt that the condition in our case corresponded with that reported by Bowers and by Rodes.

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Society Transactions

AMERICAN HEART ASSOCIATION, 1939

The opening session of the Fifteenth Scientific Meeting of the American Heart Association, held at the Jefferson Hotel, St. Louis, Mo., May 12 to 13, 1939, opened at nine-forty o'clock, Dr. William D. Stroud, Philadelphia, President of the Association, presiding.

President Stroud.—Members of the American Heart Association, friends, and guests: First of all, on behalf of the Officers and the Regional Board of Directors of the American Heart Association, I should like to welcome you to this, our Fifteenth Annual Meeting.

The papers this morning are open for frank discussion, but it has been deemed wise to limit the discussion to members of the Association and invited guests.

Unfortunately, it has been the custom for your president to make an address. I tried to escape this for your sake, but everyone seemed to think it had to be done. For the few remarks that I wish to make I have chosen the subject of "Fear in Medicine." I have been a little worried concerning this subject for many years, and feel that, as a public health organization, the American Heart Association assumes a grave responsibility with respect to the manner in which it presents to the public the subject of the prevention and relief of heart disease.

I think that everybody, naturally, is afraid of heart disease, and that there is grave danger that overemphasis of this subject, its fatality, its dangers, and so forth, may produce in this country of ours a great many introspective, apprehensive, psychotic individuals who are afraid of heart disease, but have nothing wrong with their cardiovascular system, any more than God expected them to have as they grow older.

I can remember some of the pamphlets that were distributed in 1923 or 1924 about "How Is Your Heart?" I remember one, especially, which said, "Your heart is a pump; take care of it," and showed a picture of a pump and a skeleton working at the handle. That sort of publication, I am afraid, isn't very valuable as a public health contribution. The English certainly feel that we are taking grave chances in bringing too much of this subject before the public, which is not well enough trained to really understand what it is all about.

First of all, in the last twenty years that I have been specializing in cardiovascular disease, I have seen more children and more adults—parents, that is—made cardiac cripples by the vague and serious prognostications of solicitous physicians than have been invalided by rheumatic heart disease itself. I think we all admit that, as the years go by, we realize that probably seventy-five per cent of children with rheumatic heart disease do very well until their 30's, and some until their 40's or 50's. During the intervening years—except for the twenty-five per cent who have the disease in a recurrent or acute fulminating form, and die in childhood—these patients with rheumatic heart disease need not be made invalids until they reach their 30's or 40's, when their disease will incapacitate them anyway.

As for blood pressure, a recent patient of mine, seventy years old, a rather skeptical gentleman, remarked, as I reached for the blood pressure apparatus, "That is all a racket. According to the doctor, your blood pressure is never right.

Twenty years ago they started treating me for low blood pressure, and for the last ten years they have been treating me for high blood pressure. If they had only let me alone, I should be all right.''

I believe there is something to this, except that I doubt if the treatment for low blood pressure had very much to do with his high blood pressure. As a matter of fact, most of us realize that we can do little about low blood pressure, unless there are some very obvious factors which are producing it. Usually, individuals with low blood pressure can be patted on the back and told that God has been very kind to them. They probably do not accomplish quite as much as the high-pressured individuals, but they are wonderful from the standpoint of the physician. They never feel quite right, they are always coming back to him, and they live forever.

With respect to coronary disease, it seems to me that since *Time, Fortune,* and our friends, the newspapers, are bringing this subject before the public, and most of the death notices give coronary occlusion as the cause of death, it is perfectly natural for people generally to link this condition with themselves, and feel that if their doctor tells them they have coronary disease, they are through.

I feel, personally, that it is very questionable whether a doctor—except in unusual cases—should ever tell a patient that he has coronary disease or angina pectoris, or that he has had a cardiac infarction. Sometimes it is necessary to do this to make a patient follow the proper regime.

This business has progressed to a point where—some of you have heard me tell of this experience—a few months ago a patient came in and said, ''Doctor, my family physician says I have had a coroner's occlusion.'' It does seem to me it is a little startling to be told that one has had a ''coroner's'' occlusion. It makes one stop and think. I believe—as I have said before—that if these individuals ask you, ''Do I have angina pectoris?'' you are justified in saying, ''No, you have temporary anoxemia of a portion of your myocardium.'' At least that impresses them a bit, and they usually accept it—even doctors will accept it. To an individual with a ''coroner's'' occlusion, you can say, ''No, you have a relatively permanent anoxemia of a portion of your myocardium.''

Then if you explain carefully that, as they are growing older, the stress, strain, and emotions of life place a burden on the circulation, and that, at times, if the blood pressure rises slightly above normal, because of emotion, or effort, or obesity, or indiscretions in diet, it may place a little more strain on the heart than it likes, but that if they will stay within their limitations they will have no trouble, and live out their full expectancy of life. Such an explanation will be of more benefit than telling them that they have angina pectoris, coronary disease, or coronary occlusion.

My thoughts are the same concerning unnecessary fears developed through electrocardiographic interpretations. I remember that the last thing Sir Thomas Lewis told me, in 1919, when I was working with him, was ''When you return to the United States, you must be careful in using the electrocardiographic galvanometer. Remember that the United States is a young country, and Americans are impressionable. They believe that almost anything may be accomplished through mechanical or scientific effort. If you use this machine, then look at the tracing in front of the patient, and then look at the patient and shake your head, that patient is probably a cardiac cripple for the rest of his life.''

I shall never forget when we first started taking tracings at the Pennsylvania Hospital, in 1920. I had to take them at night on the ward patients. We moved a colored patient in his bed to the heart station. You may remember the old galvanometer which reached all the way across the room. There were open batteries in the corner, and when in use it went ''phfft,'' ''phfft,'' and green lights flashed

in the darkness. I turned on the machine and the old colored fellow sat right up in bed. All I could see were his nightshirt and the whites of his eyes. He said, "Doctor, do you mind if I say a little prayer before you turn that thing on?"

Even those with more intelligence than this fellow have an awe of the galvanometer, and many of them come to you the week after the tracing has been taken and remark, "I felt ever so much better since I took that electrocardiographic treatment."

I believe that with all these machines now being sold throughout the country we must be sure to educate not only the public, but also the medical profession, as to the relative importance of the electrocardiogram. We must persuade doctor and patient, alike, that it is impossible to read from an electrocardiogram alone the last word as to the future of the cardiovascular system. I am positive that all too many physicians are attempting to read from electrocardiograms more than is justifiable.

In concluding these remarks, I should like to leave with you the thought that we must attempt to dispel some of the fear in the mind of the average person concerning cardiovascular disease. Certainly we have enough to be afraid of nowadays—social security, the administration in Washington, wars in Europe, many, many things. If we can give our patients a philosophy of life and hope and faith, I believe that we are helping them more than if we make them fearful.

General Cardiac Program

Discussion of the paper, "Possible Relationship Between Gall Bladder Disease and Cardiac Disease," by Dr. Henry L. Bockus, Dr. William D. Stroud, Dr. Paul H. Twaddle, Philadelphia, Pa., and Dr. Dolph L. Curb, Galveston, Texas.

Dr. Arlie R. Barnes, Rochester, Minn.—This is a subject that deserves a little discussion. I think Dr. Stroud is to be commended for the conservative and cautious attitude and conclusions which he has reached as a result of his studies thus far. There is some evidence to make us feel that disturbances of lipid metabolism are associated both with coronary disease and with disease of the biliary tract.

If Dr. Stroud had found that removal of an infected gall bladder resulted in reduction in the lipids, one would feel a little bit more encouraged to think that possibly such a procedure might be expected to improve disease of the coronary vessels.

Dr. Stroud very properly has emphasized the difficulties in differential diagnosis in these conditions. It is this difficulty that I think at times has given rise to the impression that the removal of the gall bladder has been a potent factor in improving the condition of the coronary arteries.

I have seen, for example, patients who had received a diagnosis of coronary disease and were put on a semi-invalid regimen for a period of three or four years. Subsequently, violent symptoms necessitated exploration of the gall bladder in each case, revealing stones and, at times, acute empyema of the gall bladder. Removal of the gall bladder in these patients dissipated the angina pectoris.

Such mistakes in diagnosis are likely to give an erroneous impression of the effect that removal of the gall bladder has on alleged heart disease.

This organization has a real responsibility in the opinion that it advances on this subject in relation to surgery. Surgeons are always looking for some new field in which to employ their art and to help us out. It is an honest attempt. If we give them reason to feel that the removal of an infected gall bladder or a diseased gall bladder gives very much promise of improving coronary disease, we are likely to see some operations performed that are not indicated. So, I am very glad that Dr. Stroud has been very cautious in his remarks, because, as far as my own personal experience is concerned, in relation to angina pectoris at least,

I have not been impressed with the fact that the removal of an infected gall bladder or a gall bladder with stones has influenced the degree or progress of coronary sclerosis.

Dr. Myron Prinzmetal, Los Angeles, Calif.—At the Boston City Hospital, Dr. Soma Weiss and I made electrocardiographic tracings routinely on patients with gall bladder colic, either with or without jaundice, but with very severe pain. We were surprised to find occasional cases in which there were definite electrocardiographic changes when pain was present, which disappeared after the gall bladder colic was over. This suggests that there may be a reflex from the gall bladder which may produce cardiac changes of some type or other, such as have been observed by Dr. Stroud.

Dr. Walter B. Hamburger, Chicago, Ill.—This subject, as Dr. Stroud well knows, is a very old one. I believe that it was about 1854 when Stokes first called attention to it.

In Chicago, Dr. Robert Babcock was the first, so far as I know, to emphasize this relationship, and for many years had many of his cardiac patients operated on. On what basis Dr. Babcock reasoned this out I don't think anyone knows.

Following his time, Frank Billings did the same thing, on the assumption, I believe, that the gall bladder served as a focus of infection, and, certainly, during the time I was with him, I saw quite a few cardiac cases in which Dr. Billings advised surgical operations on the gall bladder.

About fifteen years ago Dr. D. C. Straus and I were interested in a group of patients with extrasystoles and gall bladder disease. Several of these patients were operated on. Interestingly enough, most of their extrasystoles disappeared. As Dr. Stroud said, they may have been cured by removal of the gall bladder, or by the anesthetic, or by some other mechanism. However, in my own experience, extrasystoles and other cardiac arrhythmias do seem to have a relationship to the gall bladder.

I have under my care at the present time a woman with recurring attacks of severe auricular paroxysmal tachycardia. She has a number of gallstones which she will not permit us to remove. However, with indiscretions of diet, her attacks are very much more frequent. When she is quite careful of her diet, her attacks are relieved.

I feel that Dr. Stroud and his associates have done a fine thing in again subjecting this question to careful study. So far as I know the study of a large series such as theirs has never been made, and as a result we should find out exactly what, if any, this relationship is.

Dr. Charles N. Hensel, St. Paul, Minn.—I was very much interested in Dr. Stroud's report of the case of the woman who had experienced repeated attacks of pain (which at one time were thought by an Italian heart specialist to be due to coronary disease), who died in this country, and was found at autopsy to have relatively normal coronary arteries and disease of the gall bladder.

I can match his case with one of my own, in which, at autopsy, the findings were reversed. My case was that of a woman, a nurse, married at the age of 44 years, who had a stormy married life. I saw her first six years before her death, in a paroxysm of auricular fibrillation; at this time the electrocardiogram revealed evidence of a previous coronary occlusion. Ever thereafter she had paroxysms of auricular fibrillation, frequently associated with emotional stress, but no epigastric distress or precordial pain.

The final episode was ushered in by a state of extreme emotionalism and the complaint of a severe burning sensation in the epigastrium. The heart was normal with respect to sounds, rate, and rhythm. Her blood pressure was at the usual level of 150/80.

The abdomen was soft, and there was no tenderness over the gall bladder or in the epigastrium. Sedatives and antispasmodics were prescribed, and three days later the patient had improved sufficiently to go through with a previously planned dinner party.

She spent a sleepless night, and the next morning was seen at home, sitting up in bed, rocking back and forth, apparently in great distress, still complaining of a terrific burning sensation in the epigastrium. The heart was unchanged and the lungs were clear, but now for the first time there were definite tenderness and muscle spasm over the gall bladder. Cholecystograms showed nothing abnormal, but the patient continued to complain of burning pain in the epigastrium. Symptoms of cardiac failure eventually appeared, and the patient died three weeks after the first complaint of burning in the epigastrium.

At autopsy the gall bladder was normal, but the heart showed evidences of an old infarction in the left ventricle, plus a fresh occlusion throughout the main descending branch of the right coronary artery. Microscopically, the lesions in the freshly infarcted area were from a few days to three weeks old.

In this case then, the symptoms were suggestive of gall bladder disease, but the autopsy showed that coronary occlusion was the true cause.

Dr. Louis N. Katz, Chicago, Ill.—It is difficult to determine whether gall bladder disease perpetuates or aggravates coronary disease, but there is no doubt that reflexes come from the gall bladder which affect the heart, as was shown by Drs. Bettman and Rubinfeld at Michael Reese Hospital. In the presence of gall bladder disease such reflexes may, when coronary disease is already present, aggravate the symptoms of both the gall bladder and the heart condition.

It seems to me possible that such reflexes may actually lead to coronary spasm. While I agree with Dr. Barnes that the surgeon should not be encouraged to operate on gall bladders to relieve heart symptoms, I have occasionally seen some good results from such gall bladder operations. Pain is a sensation, and painful stimuli that may be below the threshold in the heart may summate with painful stimuli from the gall bladder, and the two together reach the field of consciousness of the patient. Little can be done operatively for the heart in such cases, but removal of the irritation in the gall bladder may make the patient more comfortable by eliminating one source of the bombardment of impulses that gives rise to pain.

Dr. Carl R. Comstock, Saratoga, N. Y.—I do not wish to prolong this discussion unduly, but very recently a patient at Saratoga (by the way, a surgeon) who had had coronary attacks for many years and also, apparently, gall bladder attacks, was operated upon.

His electrocardiogram showed no material change except left axis deviation. Cholecystograms showed numerous stones in the gall bladder. The gall bladder attacks, usually coming on at night, were quite severe, and would precipitate an anginal attack, with pain down the left arm.

He was operated on two months ago, has had no further attack, and is apparently perfectly well. His electrocardiograms are the same as before. There does seem to be some interrelationship in the distribution of gall bladder and coronary pain.

Discussion of the paper, "Factors in the Circulatory Changes Associated With Pregnancy," by Dr. J. Allen Kennedy, and Dr. C. Sidney Burwell, Boston, Mass.

Dr. Burwell.—I would like to say a word, if I may, Dr. Stroud. I want to emphasize the fact that pregnancy is a particularly suitable condition for the study of dynamics of the circulation, because every patient studied establishes her own control. She can be studied after delivery, and the results under these circumstances can be compared with the results during pregnancy.

I also think it is only proper to express to these admirable subjects who have subjected themselves to our study a vote of thanks, on the part of Dr. Kennedy and my other colleagues and myself, because they really did very good work, and they were extremely cooperative in establishing basal conditions. It is necessary, of course, to have very carefully controlled basal conditions if these observations are to be significant.

The observations that Dr. Kennedy has presented are, of course, a small part of many that have been made by many workers in the last ten years on the circulatory changes in pregnancy. Out of all of these observations, it seems that there is coming a reasonably coherent description of the total changes in the circulation in pregnancy which will enable us to guide patients with heart disease through this trying period.

I am talking now only about the burden of pregnancy itself. There is nothing in this work that bears on the burden of *labor*. But if one interprets the changes in the course of heart disease, which are brought about by pregnancy, in terms of the increased cardiac work imposed by the pregnancy, one gets a pretty reasonable explanation of the events which one sees.

One of the interesting observations that has been made by Burton Hamilton is that the incidence of the onset of cardiac failure corresponds in a large series of cases quite reasonably accurately with the calculated curve of the increased work of the heart.

Therefore, it seems to me that these observations of Kennedy and his colleagues have a very definite application to the care of patients with heart disease and pregnancy. The object of our efforts in the care of heart disease in pregnancy is mainly to protect the patient against removable burdens. The burden of pregnancy is inescapable. It is a necessary part of the body's reaction to pregnancy. The function of a physician then becomes that of helping the pregnant woman avoid other forms of cardiac overwork.

Discussion of the paper, "Cardiac Changes in Pregnancy Unrelated to the Usual Etiologic Types of Heart Disease," by Dr. William A. Sodeman, New Orleans, La.

Dr. C. Sidney Burwell, Boston, Mass.—Dr. Sodeman's very instructive paper offers many pleasant points for discussion. I hope that in the informality of the discussion period he will say what he thinks about the mechanism of these very interesting basal diastolic murmurs that appear during pregnancy and disappear during the puerperal period. I think that is a very attractive question to ask.

Now, he has emphasized how incomplete a description of the circulatory changes in pregnancy is really put on record by the observations just mentioned by Dr. Kennedy, because there are, as a matter of fact, three or four major groups of alterations in the circulation during pregnancy. One includes those that Kennedy described, that are concerned mainly with changes in the uterus and the placenta and with the immediate demands of the fetus. There are also those that nobody has mentioned yet, those of labor itself. Dr. Sodeman now points out there are also those of the puerperal period. He emphasizes that cardiac failure may appear during that period. I do not know anything about the circulatory burdens that occur during the puerperium, but I should like to ask Dr. Sodeman to comment, and to present evidence, if he has it, about the developments during lactation that produce changes in the circulation. Certainly the circulation of the breast is enormous during this period, and, also, the sudden production and excretion of a large amount of nutritive fluid must take away from the maternal body a considerable amount of accessory nutritional substances, such as vitamin B_1, for example. It is just possible that that plays a role, and I would like to ask him that question.

Finally I should like to make, in connection with his very interesting description of the occurrence of heart failure in people with hypertensive disease during pregnancy, one point of warning concerning the management of these people. It applies to a large group of cardiacs, not only to the pregnant woman. I am sure that it is familiar to you all, but it is worth emphasizing.

One of the effects of pregnancy is to increase the blood volume. One of the effects of the development of congestive heart failure is to increase the blood volume. By injecting large amounts of fluid into perfectly normal animals rapidly enough, a picture can be produced which is certainly very similar to that of cardiac failure.

Many of us have seen a considerable number of attacks of paroxysmal pulmonary edema, threatening life, follow, by a short interval, the injection, in considerable amounts, of fluid intravenously.

Now, in certain stages of hypertensive toxemic disease in pregnant women, it may be useful to inject fluid intravenously. I simply remind you that the injection of 500 c.c., or 1,000 c.c., or 1,500 c.c., of fluid into the veins of a woman who already has a large blood volume from pregnancy and increasing blood volume from advancing heart failure may very well be the final factor that precipitates the onset of serious and even dangerous cardiac failure.

Dr. Sodeman.—I know nothing about the development of these basal murmurs, Dr. Burwell. I do not think they occur as frequently as once in seventy-three patients. It probably just happened that this rare finding did occur in this group of seventy-three patients, and, if we examined 1,000 more pregnant women, perhaps we would not find one; perhaps we would find more; I don't know. The murmur disappeared in the post-partum period, and the patient has been followed for a number of years since. Nothing happened, as far as cardiac changes were concerned.

These patients with post-partum heart failure were all colored patients. They were all seen on the wards of Charity Hospital, in New Orleans. Just exactly what causes this picture, what is most important in its etiology, I do not know. Most of these patients do have some form of dietary deficiency which may have a bearing on the etiology.

As to the effects of lactation on the heart in the puerperal period, I know only one thing, and that is that the blood pressure often rises somewhat, not to abnormal levels, however, with the onset of lactation. Whether there are any other changes or not, and whether there are any other changes of importance, I cannot say.

Dr. Julius Jensen, St. Louis, Mo.—Because there is so much to be said about these last two papers, it is impossible to discuss them in detail. I would only like to point out two observations.

The first one is regarding circulatory changes during pregnancy. We, of course, are all impressed by the tremendous amount of work which has been done by Dr. Burwell and his co-workers, and we are gratified that, on the whole, their findings confirm earlier, but less securely founded, views.

Only on one point would I beg to disagree: It seems to me that the general impression is that during pregnancy the blood pressure has a tendency to rise, remaining, however, within normal limits. This applies both to the systolic and the diastolic pressures.

Whenever we are considering changes during pregnancy, I think we should draw a definite distinction between those changes which are generally acceptable for all persons and those that vary according to certain constitutional factors in the individual. Therefore, I think we should be careful not to draw too general conclusions from our observations. If we may assume that certain pathologic changes of pregnancy are merely exaggerations of physiologic changes, I can illustrate what I mean with the following observations: Hypertension is either not affected or is aggravated by pregnancy. In rare cases, however, we find an elevated blood pressure

returning to a normal level during pregnancy. It is difficult to understand how a mechanism common to all women with hypertension could have such divergent effects.

I would also like to say just a few words about functional heart disease. In general, authors and observers seem to take rather a lenient view of this so-called "functional" disorder. However, Dr. Sodeman has just intimated that there may be changes in the myocardium during pregnancy with which we are as yet but vaguely familiar, and other observations seem to point the same way.

It seems to me that we must, at least for the present, take a very cautious view as to the possible significance of any cardiac symptoms which occur during pregnancy.

Discussion of the paper, "A Study of Marked Coronary Arteriosclerosis in Patients With and Without Angina Pectoris and Related Conditions," by Dr. H. L. Blumgart, Dr. Monroe J. Schlesinger, and Dr. David Davis, Boston, Mass.

Dr. Charles N. Hensel, St. Paul, Minn.—I would like to ask Dr. Blumgart if he would care to comment, with regard to these cases of multiple occlusion of the coronary arteries, on the relationship of the Thebesian canal, and I would also like to ask him whether, with so many infarctions, the hearts are large or heavy.

Dr. H. L. Blumgart, Boston, Mass.—The heart weights of the patients with angina pectoris and multiple occlusions varied widely, from 280 to 610 grams.

The first diagram which I showed was that of a 510-gram heart, and the second was of a 350-gram heart. In the first case arterial hypertension had been present. In the second case it had not been present. In brief, then, these hearts are, of course, somewhat above normal weight, but they are not enormous hearts.

Dr. Hensel.—What about the Thebesian canal?

Dr. Blumgart.—That awaits further study. All I can say is that the material is injected into the right and left coronary arteries, and there is no evidence in our work as to the importance of the Thebesian channels or backflow from ventricular cavities.

Dr. Daniel J. Glomset, Des Moines, Iowa.—I should like to discuss Dr. Blumgart's paper in relation to the influence of anastomosis in the coronary circulation. In addition to the anastomosis which he has so beautifully illustrated, there are two other important ways in which the myocardium is supplied with blood.

First, there are frequently one or more accessory coronary arteries. Thus, a patient of mine was kept alive by a large descending right artery after his left anterior descending branch and circumflex artery had been occluded.

The second important accessory circulation comes from the pericardial and endocardial surfaces. The value of this was shown in another case of mine, in which the left coronary was occluded at its mouth. Yet the individual lived for twelve days. Necropsy revealed a vascular pericarditis. The infarct which was present involved the entire left ventricle, but the myocardium was necrotic only in the middle. The pericardial and the endocardial thirds of the myocardium were normal.

Discussion of the papers, "A Study of Marked Coronary Arteriosclerosis in Patients With and Without Angina Pectoris and Related Conditions," by Dr. H. L. Blumgart, Dr. Monroe Schlesinger, and Dr. David Davis, Boston, Mass., and "Coronary Artery Occlusion: Clinical and Pathological Correlation (Analysis of 144 Fatal Cases)," by Dr. A. M. Master, Dr. Henry Horn, Dr. Simon Dack, Dr. Harry L. Jaffe, and Dr. Leonard Finklestein, New York, N. Y.

Dr. M. A. Kugel, Miami Beach, Fla.—I must apologize for speaking at this late hour. In the eleven years of my association with the late Dr. Louis Gross, we devoted much time to the study of coronary circulation.

When we first started our studies, which are similar to those described today by Dr. Blumgart, we were impressed with the fact that the usual technical methods did not give us an accurate or complete picture of the coronary artery circulation. The hearts which we injected with barium sulphate gelatin were roentgenographed and then cleared by the method of Spalteholtz. Then, by means of dissection of the cleared specimens, we were able to demonstrate anastomoses between coronary arteries which could not have been artifacts caused by technical methods.

In this way we discovered the arteria anastomica magna, which is located in the intra-auricular septum, and provides a collateral circulation between the main left and right coronary arteries, as well as with the artery supplying the A.-V. node. A detailed description of this hitherto undescribed anastomotic vessel was published by me in the *American Heart Journal* in 1928. The vessel appears to be functionally important, particularly in cases of occlusion of the right coronary artery, in which one may find transient electrocardiographic changes referable to disturbances in the function of the A-V node. These transient electrocardiographic changes have been attributed by others to the anatomic location and the potential functional capacity of the anastomotic artery in establishing collateral circulation to the A-V node. An occlusion of the right coronary artery temporarily interrupts the circulation to the A-V node, which is normally supplied by a branch of this artery.

In general, we found that the collateral anastomotic channels enlarge in the late years of life, or there has been a partial or complete occlusion of the coronary arteries.

Finally, Dr. Blumgart brought out the important observation that one not infrequently finds hearts with multiple occlusions in the coronary arteries. The survival after many occlusions may also be dependent upon the state of the coronary artery circulation, the anastomoses, and even anomalous coronary arteries. We reported a case a few years ago of a man who had three coronary arteries; the left circumflex coronary artery had an independent origin. The right and left coronary arteries were both completely occluded at several points, and the circulation to the heart was apparently carried on by the accessory coronary artery through its anastomoses.

We refused to draw too many conclusions from purely anatomic observations, but in many of the hearts the damage was so extensive that one often wondered at the remarkable ability of the heart to maintain its circulation. The more we studied the coronary artery circulation, the less able we were to arrive at specific conclusions, but we were impressed with the fact that the heart under duress has a tremendous power of changing the course of its circulation for the better.

Dr. Blumgart.—I am very glad that the previous discusser mentioned the work of Dr. Gross and his associates, to whom we are all indebted for their splendid contributions in this field. Every investigator always hopes that there will be advances beyond what he has been able to accomplish. I think Dr. Schlesinger's method of unrolling the heart in one plane, using multicolored injection masses, and avoiding confusion by overlying vessels, is a significant contribution.

I do not want to be misinterpreted to the effect that what has been portrayed in these cases will be an invariable finding, because, after all, we have had but twelve cases of angina pectoris in this series and are still continuing our studies. Each case is a study in itself.

I was interested in hearing from the first discusser about his experience in finding collateral circulation developed through an adherent pericardium. This illustrates my previous remark, because in three cases in which we found old infarcts and an adherent pericardium no injection mass passed from the coronary circulation

through any vessels to that adherent area, as would have been expected in view of the very interesting work of Dr. Beck and his associates.

We find, likewise, that the right coronary artery is more frequently involved than any other. One not infrequently observes "infarctions at a distance," that is, infarctions of the left ventricle from occlusions of the right coronary artery. After occlusion, for instance, of the left anterior descending artery, the peripheral portion of that artery and the myocardium which it normally supplies will be vascularized by collateral circulation emanating from the right coronary artery. When the right coronary artery is then suddenly occluded, the anastomotic circulation to the left ventricle is no longer effective, and infarct occurs, for example, in the apex of the left ventricle, when the occlusion may be near the mouth of the right coronary.

It is important, in making post-mortem dissections, not to have one's mind come to rest when one fails to find an arterial occlusion in relation to the area which is infarcted.

Dr. A. R. Barnes, Rochester, Minn.—I should like to make one or two remarks in connection with what Dr. Blumgart has said, which corroborate an impression he has just given.

Dr. Burchell, working in our laboratories, has undertaken to reinvestigate the question of establishing collateral circulation by producing adhesions to the heart, either through muscle or omental grafts.

In the process of this investigation, after having attached either muscle or omental grafts to the myocardium, the coronary circulation was interrupted by stages until all three branches were finally occluded, and the animal was allowed to live.

Strangely enough, he found exactly what Dr. Blumgart found, that if these vessels are occluded one at a time, the remaining branches establish a collateral circulation of their own which is sufficient to maintain the heart in excellent function, and that function is derived from these anastomoses and not from anastomoses that are the result of the attachment of muscle or omentum to the heart.

Injection either from the heart side or from the side of omental or muscle graft did not show any appreciable amount of circulation going through these omental or muscle grafts.

Moreover, after all three branches, or branches of three main vessels, had been interrupted, the dog was able to carry out a normal amount of work on the treadmill because of this sufficient collateral circulation. If he now interrupted the grafts by cutting them off, there was no loss of the dog's ability to carry out exercises.

Dr. Arthur M. Master, New York, N. Y.—I was interested in the case that Dr. Blumgart described in which there were nine old occlusions. Our pathologists, particularly Dr. Horn, find it difficult to make a diagnosis of old occlusions. I know they do occur, and it may be that Dr. Blumgart's method is an improvement on routine pathologic procedures. We have all had patients with many occlusions. I have had two patients with five closures, typical clinically and electrocardiographically, and they are both alive at the present moment.

I was interested to hear Dr. Blumgart talk about postoperative shock as a cause of coronary occlusion. We have noted that coronary occlusion does occur following an operation.

Mention was also made of the fact that, if a patient has severe coronary sclerosis and angina pectoris, rest is extremely important. I want to emphasize, however, that nobody has shown that effort will produce another occlusion, although I am sure it may cause death by coronary insufficiency. I also want to emphasize that term "coronary insufficiency," because I think that that is entirely different from

coronary artery occlusion. That is why I would prefer to use the term "coronary artery occlusion with cardiac infarction," than merely say "myocardial or cardiac infarction."

Discussion of the paper, "Production of Pressor Substance by Totally Ischemic Kidney," by Dr. Alberto C. Taquini, Buenos Aires, Argentina.

Dr. Louis N. Katz, Chicago, Ill.—The results which Dr. Taquini has presented on the direct demonstration of a pressor substance have not been confirmed entirely by others. Many investigators, including my associates and I, have failed to find any evidence of a pressor substance in the blood coming from an ischemic kidney.

In our work, we perfused unanesthetized, bilaterally nephrectomized dogs with the blood from dogs made hypertensive by the Goldblatt technique. Over a period of twenty-four or more hours, we replaced the blood of the nephrectomized non-hypertensive animal with the hypertensive blood two or three times, without any demonstrable elevation of blood pressure. When we perfused the hind limb of anesthetized dogs with the blood of anesthetized, hypertensive animals, the only effect obtained was dilatation, not constriction.

We all realize that everything points to a pressor substance, but I wonder whether the results of Taquini are not due to the liberation of renin by the severe ischemia, a sort of extraction in life?

Dr. Taquini (closing).—We have tried to produce muscle constriction with blood from the general circulation without success, but with blood taken directly from the kidney we obtained a wonderful muscle-constricting action. It seems that the blood from the totally ischemic kidney contains more of the pressor substance than that from the partially ischemic kidney, because when I tried to produce hypertension in the dog by direct injection of the blood from the ischemic kidney by another method, I failed. But with the blood from the previously ischemic kidney, I obtained results in all of the cases.

I have the results here, and I will read some of them. This is the rate of perfusion in the preparation of Löwen Trendelenburg.

In the first experiment, the number of dogs injected with Ringer's solution was 60; with plasma from the renal vein of a normal kidney, 66; with plasma from the totally ischemic kidney, 14. That means a diminution of about 65 per cent.

In the second experiment, the number of dogs injected with Ringer's was 71; with plasma from the renal vein of a normal kidney, 75; with plasma from the totally ischemic kidney, 2; making a diminution of about 95 per cent.

In the third experiment the number of dogs injected with Ringer's was 56; with plasma from the renal vein of a normal kidney, 63; with plasma from the totally ischemic kidney, 7, and so on. All of the experiments gave the same results.

We don't think that there may be changes in the secretory function, because, in the experience of Graffman and Kinney, only blood from the previously ischemic kidney produced, in the same dog, a marked pressor effect. The injection of 100 c.c. of blood from the normal kidney does not produce any change in the blood pressure of the animal, but with blood from a kidney previously made ischemic there was a great hypertension.

Discussion of the paper, "Clinical and Experimental Studies on Quinidine: With Clinical Application as to Method of Treatment in Auricular Fibrillation," by Dr. Samuel A. Weisman, Minneapolis, Minn.

Dr. Lewis A. Conner, New York City.—It seems to me that many of the points that Dr. Weisman has emphasized are fully deserving of such emphasis.

I have thought that we had all been convinced by this time that quinidine was not dangerous, in the ordinary sense of that word; and, if used wisely, was a valuable and relatively safe drug.

I am not sure that the method of giving quinidine in several doses close together during a part of the day, with nothing after that until the next day, is theoretically a satisfactory way.

Sir Thomas Lewis, as you know, back in 1925, I think, showed that, in order to restore the normal rhythm, certain changes in the circus movement had to be produced by the quinidine and maintained for a certain time. As I recall it, he showed that the effect of a single dose of quinidine was not longer than four, or five, or six hours. The inference was that one ought to maintain the quinidine effect by doses throughout the twenty-four hours, rather than having a long free interval at night.

Certainly, as I have used it, we have always continued the quinidine throughout the 24 hours. If we were using it in fairly large doses and expecting to get results within a very few days, two or three days, perhaps, we have always given it continuously through the night at four-hour intervals. Whether that is necessary or even desirable, I don't know.

There can be no doubt of the desirability of restoring the normal sinus rhythm in a great many cases, probably in most cases, of auricular fibrillation, but I should like to raise the question whether that applies to every case of auricular fibrillation. Of course, the ones that are most doubtful are those of advanced mitral stenosis. My feeling is that they are better off, often, without normal rhythm.

In the first place, the normal rhythm isn't likely to be maintained very long. There may be exceptions; doubtless there are exceptions to that rule, but a patient with high-grade mitral stenosis and auricular fibrillation does not very often, I think, maintain a normal rhythm once the quinidine has been given and has been effective.

But even if it does restore and maintain the sinus rhythm, I still raise the question whether that is a desirable thing in these advanced cases of mitral stenosis.

I don't know of any type of patient that is harder to treat effectively than just such a one with mitral stenosis who has *not* developed auricular fibrillation. The effects of digitalis are far less striking and satisfactory than when fibrillation is present.

If, with fibrillation, one can maintain the rate at 60 or 65, the patient usually is much better off than if he has sinus rhythm with a heart rate of 80, 90, or 100.

Dr. H. L. Smith, Rochester, Minn.—In treating any patient who has auricular fibrillation, it must be remembered that we all have seen a great number of patients with chronic auricular fibrillation that has continued for many years, yet these patients have been able to live and be reasonably active in spite of this fact.

I quite agree with the speaker that the occurrence of emboli as a result of administering quinidine has been greatly overemphaasized.

I believe that there are certain patients to whom it is advisaable to administer quinidine, such as, first, patients who have the so-called idiopathic auricular fibrillation, or patients who have fibrillation without any other evidence of organic heart disease; second, patients who have a minimal amount of heart disease and do not have fibrillation of long duration; and third, patients suffering from hyperthyroidism who continue to have fibrillation after thyroidectomy.

I question the advisability of attempting to establish normal rhythm in patients who have serious organic heart disease, and especially in those who have hypertensive and arteriosclerotic heart disease with marked hypertrophy.

I believe the greatest danger to such patients, if quinidine is administered to them, is that of sudden death. Sudden death in such instances is probably the result of depression of both the sinoauricular and auriculoventricular nodes for a

sufficient period to produce death. This danger must be considered seriously and weighed against the benefit that the patient receives when normal cardiac rhythm is re-established.

Dr. Thomas Lee, Washington, D. C.—I rise chiefly to ask Dr. Weisman if he would explain to us how it is that patients with auricular fibrillation whose heart rates may be reduced, as I believe they can in nearly all cases, to a reasonable figure, 60, 70 or 80, if you wish, lose as much as 75 per cent of their cardiac efficiency because of their fibrillation. The heart muscle is the same. One must revert, then, to the question of the advantage that is gained by having the auricles add their propulsive force to the circulation. Although it is very easy to conceive that it may be 15 per cent, and doubtless is sometimes more, I cannot quite see how the difference would rise to 75 per cent in the same heart.

I would feel with Dr. Weisman and the other speakers that it is very advantageous in most cases to have normal rhythm instead of auriclar fibrillation. However, it cannot always be done.

I would like to bring forward the point that many patients can go on continuously with auricular fibrillation with very good function for a long period of time. As a matter of fact, I am reporting tomorrow, at a meeting of one of the other societies, a case in which fibrillation has been present for thirty-five years, which is, I believe, the longest duration that has been reported in medical literature; the patient, now nearing 70 years of age, has been very active all of that time. His ventricular rate has been kept between 70 and 80, and his functional capacity has been very good.

I don't wish to imply that I do not use quinidine very frequently. I think it is most effective in many cases. I think that in the type of case Dr. Smith has referred to, that is, in younger patients without very serious organic heart disease, it is most desirable to use it. But I want to emphasize the fact that in those cases in which its use is undesirable, especially including those which Dr. Conner has just spoken of, and those in which it is not effective, the heart may perform its function very satisfactorily, as has been brought out more and more in recent communications, for a long period, in spite of auricular fibrillation.

Dr. Joseph B. Wolffe, Philadelphia, Pa.—Many studies have already been made and reported on the use of quinidine in auricular fibrillation. A number of years ago we divided our cases of auricular fibrillation at the cardiac clinics of Temple University and Mt. Sinai Hospitals and treated some of the patients with maintenance doses of digitalis, while to others we gave quinidine in a manner similar to that which has been so well described by Dr. Weisman. Strange to say, we had very fine electrocardiograms to show as a result of the quinidine therapy. We restored normal rhythm in a great many cases, but we were amazed that over a period of time the mortality was greater in that group than among those who had been taking only maintenance doses of digitalis and, occasionally, quinidine, but without any idea of restoring normal rhythm. Particularly was that true of patients who suffered from arrested rheumatic heart disease with mitral stenosis.

We feel, therefore, that it is extremely important to consider the etiologic factor, rather than the disturbed physiologic state, before using quinidine.

No one doubts that quinidine is a most valuable drug. In cases of auricular fibrillation caused by thyrotoxicosis, in which the underlying cause has been eliminated, or in cases of paroxysmal auricular fibrillation either of unknown origin or caused by an autonomic disturbance, quinidine will aid in restoring the normal sinus rhythm, which greatly benefits the patient. On the other hand, in mitral stenosis we found it best to use it only as an adjunct, if necessary, together with digitalis, but by no means to attempt to restore normal rhythm. As a matter of

fact, we feel that auricular fibrillation is a protective mechanism in many cases of mitral stenosis, like soldiers breaking step while crossing a weak bridge.

If the pulse deficit and the heart rate are controlled, patients with auricular fibrillation may lead fairly long and useful lives. Strange as it may seem, very often at the bedside of a patient with advanced mitral stenosis who failed to respond to the ordinary methods of therapy, I have wished that we had some drug to induce auricular fibrillation.

Dr. Weisman (closing).—The greatest danger of embolus formation occurs in auricular fibrillation, more so, perhaps, than after normal rhythm has been restored.

Sir Thomas Lewis' experimental studies of the effect of quinidine on dogs showed that the maximum effect of the drug on the heart took place in about two hours. It was about twelve hours before the effect of quinidine was entirely gone, and almost twenty-four hours before the heart rate returned to normal. So, quinidine does have a prolonged action, but we do not know yet whether it is best to give the quinidine every hour or every two hours. So far, our work indicates that giving it every hour is very satisfactory.

In cases of mitral stenosis it is most difficult to restore to normal rhythm, but once normal rhythm returns, the patients seem to get along satisfactorily.

Dr. Smith: Many reports in the literature warn us against giving quinidine to old people, to patients with coronary disease, and to patients with mitral stenosis of long standing. Korns, of Cleveland, now of Iowa City, some years ago, in reporting his studies on quinidine, showed that some of the best results were obtained in old people, those with coronary disease, and patients who were more or less cardiac invalids. We, too, found that the most spectacular results were obtained in old people and in those with coronary disease and beginning signs of cardiac decompensation.

Dr. Lee brought up the question of the efficiency of the heart after normal rhythm had been restored. This has been studied time and time again by many investigators, among whom were Eyster and Swarthout, Smith, Walker, Alt, and, more recently, Kerkhof, of Minneapolis. Eyster and Swarthout showed that the efficiency of the heart diminished from 20 to 70 per cent when auricular fibrillation was present.

Dr. Kerkhof made a study of the cardiac output of a group of patients with mitral stenosis and auricular fibrillation before and after normal rhythm was restored. He found that there was an average increase of about 25 per cent in the cardiac output after normal rhythm was re-established.

Discussion of the paper, "Importance of Restriction of Salt as Compared to Water in Cardiac Failure," by Dr. Henry A. Schroeder, New York, N. Y.

Dr. Walter B. Hamburger, Chicago, Ill.—In reference to these very interesting observations on the restriction of salt in cardiac failure, I should like to ask Dr. Schroeder whether he believes the sodium or the chloride ion is the effective agent.

In his reply I would be interested to know what potassium chloride, as a substitute for sodium chloride, might do and also what role ammonioum chloride, which is given with the mercurial diuretics, may play.

Dr. Schroeder (closing).—We have made no observations on the relative effect of sodium and chloride ions. It is known, however, that the sodium ion is important in edema due to low plasma proteins. The edema of congestive heart failure, although of different etiology, may be of similar mechanism, that is, a filtration edema. It is possible that the same factors with regard to the sodium ion are at work in both types of edema. No attempt has been made to evaluate the effects of the potassium and the ammonium ion.

Discussion of the paper, "The Clinical Use of the Lag-Screen Electrocardiogram," by Dr. Graham Asher, Kansas City, Mo.

Dr. Howard B. Sprague, Boston, Mass.—I should like to attest the excellence of this instrument that Dr. Asher has devised. I had the opportunity of seeing and using his model just before it was decided to put it into commercial production, and to act as a consultant on technical matters in the manufacture of the machine.

I think he has mentioned to you only the early immediate possibilities of the use of this instrument. Its usefulness is similar to that of the fluoroscope, as compared with the teleoroentgenogram. One of the other possibilities that could be mentioned is the routine checkup examinations of patients in offices, when one has a series of electrocardiograms on the same patient and does not feel that it is necessary to fill up the files with a lot of routine electrocardiograms. Another is the possibility of rapidly examining large groups of people, such as students, men for the army, insurance applicants, or the like.

It is now possible to stop the machine temporarily (it gives a very clear tracing), and to superimpose both time and amplitude lines for a short period on any part of the tracing that you wish. This is done by illumination through the back of the screen.

The two criticisms that I have heard about this instrument are that anyone who can interpret electrocardiograms, and, as Dr. Asher says, only such a person should use the machine, can get a pretty good idea of what is going on by watching the string shadow in the modern, portable instrument. But this instrument is far better.

The other criticism is one that I just recently heard. It was said that this machine made it so easy for the consultant to make the diagnosis at the bedside that it embarrassed him because he had to decide what he was going to do immediately, and could not get back to his office to telephone later what the record showed.

Dr. Asher (closing).—I want to thank Dr. Sprague for his kind criticism. I do, however, want to say that the making of this thing reminds me of the title that Dr. Hertzler first used for "The Horse and Buggy Doctor." The title originally was "Too Dumb to Quit."

I think that sometimes, as we worked with these things, the knowledge of his struggle made us keep on, and perhaps we were too dumb to quit.

Discussion of the paper, "Ligation of Patent Ductus Arteriosus," by Dr. John P. Hubbard, Boston, Mass.

Dr. C. Sidney Burwell, Boston, Mass.—I should like to make two observations concerning this very interesting and important paper of Dr. Hubbard's.

The first is to put on record my admiration for the imagination, determination, and skill which made it possible for these workers to conceive and develop this method of treatment.

The second is to say just a word about one of the points made in the justification of this surgical procedure.

Dr. Eppinger, in my laboratory, has had the privilege of analyzing blood obtained from the pulmonary artery and the adjacent aorta of two of these patients at the time of operation. The analysis of this blood has, for the first time, permitted a demonstration that the shunt, which we all have believed to be present, actually occurs. It has also given us some rather surprising information as to the magnitude of this shunt.

Under the conditions of operation, with the anesthesia and the other phenomena attendant upon operation, in the two patients that have been examined it can be

shown that approximately three-quarters of the blood which comes out of the left ventricle through the aortic valve immediately flows back into the lungs by way of the patent ductus arteriosus.

Such an extraordinary loss of blood from the arterial system can be met in only two ways. One way is to subtract this from the peripheral circulation. When that occurs, as Dr. Hubbard suggests, if it occurs over a long period of time, interference in growth may result.

The second way, and, from our observation so far, apparently the main way, is for the left ventricle to increase its output greatly. A great increase in the output of the left ventricle obviously implies a corresponding, or nearly corresponding, increase in the work of the left ventricle, and presumably this explains the limitation which these patients have with respect to exercise and other activities.

It seems to me that these measurements support the contention of Dr. Hubbard, namely, that a patient with a large, patent ductus arteriosus may justifiably be operated upon in an attempt to relieve the heart of this large increase in work.

Dr. William J. Kerr, San Francisco, Calif.—It is indeed a thrilling thing to live in a time when members of our profession have the imagination and the technical ability to perform this operation.

Since last summer, when Dr. Gross performed this first operation for Dr. Hubbard, we have hoped that we would be able to contribute something in this direction. About three months ago the opportunity presented itself to treat a young woman, 26 years of age, who was already beginning to have cardiac failure because of this anomaly. We felt quite certain that there were no other serious abnormalities in the circulatory system. We were bold enough to attempt it, Harold Brown, of San Francisco, performing the operation.

We found, however, that in the adult it may be a little more difficult technically because the ductus lies so deep in the chest. We discovered something which is unusual in connection with this problem. This patient developed collapse of the lung and pneumonia and died subsequent to the operation. At the time of operation, we were not certain that we had tied off the ductus. At autopsy it was found that there was no ductus at all, but that there was a fistula, 7 mm. in diameter, directly between the aorta and the left branch of the pulmonary artery. I think this variation is quite unusual, and it is possible that others like it will be encountered.

I understand that five patients have been treated surgically at the Children's Hospital in Los Angeles by Dr. Dolley, with very successful results in four, and a subsequent complication resulting in death in the fifth.

One of the things Dr. Hubbard brought out, which I would like to emphasize, is that under the fluoroscope one may see tremendous pulsations of the pulmonary artery throughout the entire pulmonary field. This is particularly striking when there is a large fistula.

Another thing of interest is in regard to the murmur. It is said that there is a systolic accentuation of the humming-top murmur in these patients. We have been able to show, however, that this murmur occurs about one-fifteenth of a second after the first sound; this can be brought out by means of the symballophone.

Discussion of the paper, "Changes With Age in the Electrocardiogram in Adult Men," by Dr. Alfred E. Cohn, Dr. William Hall Lewis, Jr., and Dr. A. Garrod MacLeod, New York, N. Y.

Dr. Louis N. Katz, Chicago, Ill.—In regard to this fundamental work, I wish to ask whether or not it is justifiable to include as normal, in such a group, individuals with abnormalities in their electrocardiograms such as prolongation of the P-R or QRS intervals beyond normal limits, or inversion of T_1 or T_2. Until such time that

it is shown that these particular variables can be considered normal, is it not better to consider them, not as normal phenomena of senescence, but rather as abnormalities, even in the aged? After all, at every age abnormalities in the electrocardiograms occur which are not necessarily associated with symptoms and signs. In other words, what is senescence? When is it normal? When is it abnormal? Consequently, I would like to have Dr. Lewis discuss the justification for including the four or five individuals with abnormal electrocardiograms in the normal group of aged persons.

Dr. Lewis (closing).—I should like to answer Dr. Katz's question by remarking first that what we now consider abnormal may, when we have further knowledge about the exact events in senescence, come to be considered normal.

This study has been carried on for some time, and reports have been already published about it. I, myself, was responsible for the selection of a group of men. None was an inmate of an institution. Every one was active. Some of the men (I think I might describe their clinical state to represent how normal they were) had definite histories of activity over long years of life. The oldest man, 101 years of age, was the oldest living Yale graduate. One man, 91 years old, was extremely well known for his investigations, or for his work, as a cartographer with the United States Geological Survey in the West in 1866 and 1867. At the time of his examination, in 1934, he had the preceding summer and the succeeding summer arranged to go out to the Middle West again and retravel the old Oregon Trail.

The observations that have been carried out included not only the electrocardiographic examinations, but also records of blood pressure, urea clearance, and the size and shape of the heart in the teleoroentgenogram, in order to give us as much detail as possible about the effects of senescence on the various biologic functions.

In regard to the unusual electrocardiograms, or what have heretofore been considered unusual electrocardiograms, I have some subsequent data on some of these men, and I might make a few points about them.

Let us take one man who was 67 years of age at the time of his examination, in 1934. He was active, healthy, and, according to the various other tests of biologic function, such as the urea clearance and size and shape of his heart, normal. However, his electrocardiogram showed an inverted T_1, measuring 1.2 mm., and an inverted T_2, measuring 1.4 mm. He had had no symptoms indicating heart disease of any form, but his electrocardiogram, as I said, showed these abnormalities.

He came for examination, of his own accord, about one month ago when I had an opportunity to see him in my office. He had retired from his official positions in 1934 at the age of sixty-seven. He had continued his many activities, however, in the five years since his examination. He had traveled all over the world on numerous missions as the active head of the International Council of Churches. He said he had never been busier in all his life. He was the former head of the International Y.M.C.A.

Another man who had a prolonged QRS interval, measuring, as I recall, 0.14 second, but who gave no history of cardiac symptoms, has also been very active as a treasurer in the Y.M.C.A. organization for the past five years, and he is perfectly healthy.

On the other hand, there were men who, at the time of the selection of this group, had symptoms of heart disease, such as pain on effort, and yet had normal electrocardiograms. They were not included in the group; not long afterward, it was found that they had died of heart disease.

So, as a matter of fact, it may turn out that certain criteria established by instruments of precision, which we have heretofore considered abnormal, may be, after all, normal when we come to deal with individuals over 65 years of age.

Section for the Study of the Peripheral Circulation

Discussion of the paper, "The Saphenous Valves in Varicose Veins," by Dr. Edward A. Edwards and Dr. Jesse E. Edwards, Boston, Mass.

Dr. Geza de Takats, Chicago, Ill.—I do not feel at all competent to discuss this excellent paper from the histologic standpoint.

Clinicians, of course, have long recognized that the valves in varicose veins are insufficient and that the flow of blood is reversed when the patient is standing. In some previous work, the authors have clearly demonstrated the valvular shrinkage and insufficiency which follow phlebitis. Today they showed with painstaking care, after studying a large number of patients, that in the uncomplicated, noninfected varicose vein the dilatation of the wall is the cause of a relative insufficiency.

Whether this weakening of the wall is due to a congenital defect in the muscular or elastic elements, whether it is due to postural strain on a circulatory system which was originally designed for a four-footed animal, or whether the connective tissue of certain asthenic individuals is such that it gives way more readily to increased venous pressure, cannot be decided by purely morphologic studies.

I believe, however, that one can find evidence for the existence of any one of these possibilities. Thus, in ligating veins at the saphenofemoral junction, one sometimes finds saccular venous aneurysms with a perfectly well-developed muscular wall surrounding them. One cannot help suspecting that there are segmental defects in the wall. In other cases, in spite of marked elongation and dilatation of the saphenous system, there is a pronounced muscular hypertrophy at the upper end of the saphenous vein, which is the normal response to venous hypertension. Again, in other patients, stigmas of an asthenic habitus, such as a long, narrow chest, a sharp costal angle, visceroptosis, and flat feet, signify that we are dealing with a diminished tonus, an inferior make-up of connective tissue.

I should like to ask the authors whether they have found any evidence of absence or rudimentary development of valves in the perforating veins or the femoral vein above the saphenofemoral junction, as described by Turner Warwick. In our clinic we have watched for the incompetence of the femoral valve following straining or coughing and have found it in approximately 10 per cent of all cases. Absence of this important valve above the saphenofemoral junction is said to be found not infrequently at autopsy. It is the only competent valve between the right heart and the saphenous vein. Fluctuations of abdominal venous pressure can be readily transmitted to the lower extremities if this valve is incompetent.

It is to be hoped that the authors will extend their studies to the valves of the iliofemoral veins and, perhaps, also to the sphincters in the caval system, such as have been described in the renal and hepatic veins. These sluice mechanisms open and close a large reservoir, and their varying tonus may be as important for venous return as the valves are.

Their present study conclusively demonstrates that the valvular insufficiency, as far as the upper saphenous valves are concerned, is due to dilatation of the wall of the vessel, and not to local inflammation, degeneration, or rudimentary development of the valves themselves.

Discussion of the paper, "The Mode of Development of Collateral Venous Circulation in the Extremities," by Dr. Ross Veal, Washington, D. C.

Dr. Norman E. Freeman, Philadelphia, Pa.—As before, Dr. Veal has made a very splendid contribution to our knowledge and understanding of the problems of the venous circulation associated with acute obstruction.

I would like to take up this discussion under three headings. The first is the question of the reaction of the blood vessels to the initial closure or the initial thrombosis. That apparently sets up quite a vigorous arterial and venous spasm. Dr. Veal has called attention to the arterial spasm, which may be of such magnitude as actually to cause gangrene. I have observed one patient who has developed gangrene because of spasm following acute venous thrombosis.

Two other patients whom I have seen also developed extremely severe arterial spasm as the result of acute thrombophlebitis.

The second point is the venous spasm. We have been interested, in Philadelphia, in observing these patients with their acute thrombophlebitis, and we have seen unmistakable evidence of acute spasm of the veins in the periphery distal to the site of thrombosis.

Now, our interest in this grew, to a certain extent, out of the observation that, associated with acute thrombosis of the vein, the temperature of the affected extremity frequently was higher than normal. We all recognize the fact that one of the signs of phlebitis is a hot skin. Hot skin means increase in blood flow. Heat must be brought from the body to the periphery and deposited there in order to have the skin hot. We know that the venous pressure is increased, but it is quite interesting that with an obstruction to the venous return there is actually more blood flowing out to the part and, therefore, there must be more blood flowing back from the part.

In view of these facts, there must be collateral venules available even during the acute stage, through which blood could come back from the extremity affected by thrombophlebitis.

We therefore decided, since we knew that blood was flowing out in increased amounts, that by compression of the veins by the application of a tight plaster we would be able to speed up the flow in the channels which were open and prevent stasis of blood in large, dilated veins with very high pressure.

Our results have been just as splendid as those which Dr. Veal obtained by the use of his Unna boot from the toes to the knee. We have used the Ace bandage and bound the extremity from the toes to above the knee.

As far as the character of the fluid is concerned, Dr. Veal spoke about the fact that when the lymphatics are blocked an increase in edema formation occurs. One other fact should be mentioned, namely, that when there is an inflammatory reaction of the tissues in the lower leg, as, for instance, after acute thrombophlebitis, there will be an outpouring of fluid which is rich in protein. The blood vessels are damaged, and when the fluid is examined, one finds that the protein content is between 2 and 4 per cent. That is subcutaneous fluid in the area of tremendous edema, after an acute thrombophlebitis.

If we can prevent those vessels from releasing this protein-rich fluid, we will do much to decrease the fibrosis and resultant incapacity after the period of recovery.

Dr. Geza de Takats, Chicago, Ill.—There are certain points in Dr. Veal's excellent paper which I believe should not go undiscussed. One is the sudden increase in venous pressure on exercise in cases of axillary thromboses. These patients have definite intermittent "claudication" of the upper extremity when they exercise their arms. It seems to me that the high venous pressure would be capable of explaining that.

In the lower extremity, the intermittent claudication is usually regarded as an indication of impaired arterial circulation, but when a patient with axillary thrombosis exercises his arm, the pain becomes, very shortly, unbearable. We have observed that again and again.

Another point is that this edema must be due, at least in part, to certain vascular reflexes originating from the thrombosed vessels. In two instances, in patients who

had been in bed with the arm elevated, we were able to get rid of this edema after stripping the thrombosed vein, an observation which, of course, has been made by Leriche and others.

The most important point, however, I think, is the idea that these patients with a deep thrombophlebitis can get up in a few days. Dr. Veal did not make it quite clear, and I wish to ask him just when he allows them to get up. Certainly he does not let them stay in bed for four or six weeks. In a few cases we have allowed these patients to get up, wearing their elastic support from the toe to the groin.

It is my impression that the incidence of embolism is certainly not higher in this group than it is among the patients who are made to stay in bed for a long time.

In a recent survey of our cases of pulmonary embolism, we found that in only 2 out of 100 was there a frank, deep thrombophlebitis. Therefore, it seems to me that, if a patient should have pulmonary embolism after getting up early, the chances are that he would have had it under any circumstances. In fact, our two patients who did develop pulmonary embolism were immobilized for as long as eight weeks.

Dr. Irving S. Wright, New York, N. Y.—It has been our observation that allowing patients with thrombophlebitis to be up and about has aggravated the local symptoms in many cases, even though embolism did not seem to occur oftener. This seems more likely to occur when the superficial veins are involved.

I would like to ask Dr. Veal's opinion regarding this.

Dr. Veal (closing).—I am of the same opinion as Dr. de Takats, namely, that these patients should be gotten out of bed very promptly. In most of these cases the patient has been operated on, and one must therefore wait until the postoperative course is at such a stage that he may be allowed out of bed with safety.

As for the local symptoms, if the boot is placed high enough and firm enough we have not yet found that it has caused any pain or increase in other symptoms. It seems that the heat kept in by this boot tends to release the spasm of the arteries and veins, and it certainly lessens the edema.

One other point I did not bring out. During the acute stages, before one can let the patient out of bed, there are likely to be increased edema and some cyanosis. We have found that alternating the position of the bed tends to relieve this edema and cyanosis. We elevate the foot for an hour and then reverse the procedure and elevate the head. It certainly brings about some relief and prevents the formation of too much edema.

Discussion of the paper, "The Significance of Vascular Hyperreaction, as Measured by the Cold-Pressor Test," by Dr. Edgar A. Hines, Jr., Rochester, Minn.

Dr. Irvine H. Page, Indianapolis, Ind.—Dr. Hines has, I think, developed an impressive body of evidence in the past six years. The effort to estimate the responsiveness of the vascular system by some method such as the cold-pressor test has aways seemed to me to be desirable. Among the many methods proposed, none seems to be simpler than Dr. Hines' test. Probably it is actually a combined cold and psychic stimulus, because immersion in water at 4° C. is quite painful. I have seen many patients complain bitterly of the cold when the hand was immersed in ice water.

Obviously, the important question to be answered is whether or not, in fact, the cold-pressor test enables us to predict the development of hypertension. In favor of this opinion is chiefly the observation that more cases of hypertension occurred

in the small number of hyperreactors originally studied by Hines and Brown than in the hyporeactors. As Hines points out, we shall have to wait ten years before this can be conclusively established.

It is alarming to hear that if both parents are hyperreactors, 95 per cent of the children react similarly. This would almost surely doom the children to hypertension. I think Dr. Hines would agree that, while this may be the trend, it by no means necessarily seals the children's fates. I have, and doubtless the rest of you have, seen persons, both of whose parents had hypertension; yet they were without a sign of it. In one family I watched for its appearance confidently for seven years, with no success, although the children had entered the fourth and fifth decades.

It is needless for me to point out the importance of this work. It is worth suggesting that physicians apply this test to large groups of patients who can be followed from year to year, so that the question of whether or not this test foreshadows the future may be answered definitely. But under no circumstances should the patient be told the result. Perhaps the result should be sealed in an envelope, like election predictions.

My personal feelings are mixed, regarding this test. I have employed it with varying success. Now that I have seen Dr. Hines' figures, I sense that the burden of proof is gradually being shifted to the disbelievers. Whatever one's personal opinions in the matter, sufficient evidence has been presented to demand an unequivocal answer, and the rest of us should lend a helping hand.

Dr. John H. Miller, New York, N. Y.—Last year Dr. Maurice Bruger, of New York Postgraduate Hospital, and I became interested in the possible application of this cold-pressor test as a clinical method for differentiating essential hypertension from the secondary forms of hypertension, particularly the type seen in chronic renal disease.

A group of normal hypo- and hyperreactors was also studied for purposes of statistical evaluation. We followed the procedure of the test as outlined by Dr. Hines, except that we used a recording sphygmomanometer instead of the auscultatory method. I will not go into all of our results, as they will appear later in the AMERICAN HEART JOURNAL, but the responses of our normal hyporeactors and hyperreactors, as well as of the patients with essential hypertension, closely paralleled and confirmed the observations of Dr. Hines.

One not infrequently encounters a patient with hypertension and urinary abnormalities, in whom it becomes very difficult to determine whether the elevation of blood pressure is due to kidney damage, or vice versa.

In our patients with proved nephritis, 73 per cent of whom had hypertension, we found that the mean response to the cold stimulus was 16.2 mm. in systolic, and 12.6 in diastolic, pressure. These figures, though slightly above the mean response of the normal hyporeactor group, showed no appreciable deviation when compared statistically. I note that they are within 1 mm. of the mean response for the entire normal group given by Dr. Hines.

While we were carrying on our studies, Allen and Smirk reported their results with this test and showed that, unlike most patients with essential hypertension, patients with nephritic hypertension do not exhibit a hyperpressor response to cold; however, their patients with renal hypertension gave a response lower than the normal hyporeactor group.

In view of this work and our results, we concluded that a hyperreactor response in a patient with arterial hypertension would exclude chronic renal disease as the cause.

We do not feel that the converse of this holds true, as we found that 24 per cent of our patients with essential hypertension gave a response within the limits of normal. This group must be the subject of further investigation.

In order to determine, if possible, the factors causing this lack of hyperreactor response in some patients with essential hypertension, we subdivided this group according to the degree of arteriosclerosis present, the presence or absence of albuminuria, the duration of hypertension, and, finally, according to age.

It was found that those individuals exhibiting moderate to severe degrees of arteriosclerosis, those having albuminuria and secondary manifestations due to nephrosclerosis, and, finally, those between the ages of 65 and 75, had an appreciably smaller response to cold than did those who had few or none of these complications or were younger.

However, we do not feel that these factors alone account for the lack of a hyperreactor response in some patients with essential hypertension.

As Dr. Hines has stated, it will take another ten or twenty years to ascertain whether or not essential hypertension occurs among the present normal hyporeactor group. Should this occur, we feel that it may possibly explain the small percentage of normal responses encountered in the essential hypertension group.

Dr. Hines (closing).—I appreciate Dr. Page's and Dr. Miller's discussions of my paper. I agree with Dr. Page that the general use of the cold-pressor test to predict the future development of hypertension is not indicated at the present time. As I stated previously, the main purpose of this presentation was to show that a prehypertensive, or an antecedent stage, of essential hypertension exists. Unquestionably, it will take another five or ten years to determine definitely how many of the hyperreactors will develop essential hypertension. Furthermore, the test does not indicate when hypertension will appear or how severe it will be if it does. I think that we have enough phobias without adding the phobia of high blood pressure.

My experience with the test in patients with chronic nephritis, although more limited than that of Dr. Miller, is similar to his. I have not found the reactions in patients with renal disease to be as marked as in those with essential hypertension.

Discussion of the paper, "The Cardiac Factor in Experimental Vasomoter Hypertension," by Dr. Norman E. Freeman and Dr. W. A. Jeffers, Philadelphia, Pa.

Dr. J. Murray Steele, New York, N. Y.—I have only one or two words to say. It is an extraordinarily interesting piece of evidence for the existence of a choice of innervation in an organ; without adrenalin, the sympathetic nerves seem to be able to do for the heart what it needs; without the sympathetic nerves, adrenalin seems to be able to arouse the response.

There is a large number of factors involved in the hemodynamics of this situation. Decrease in tone of the heart muscle, whether due to lack of adrenalin or to failure of the nervous mechanism, might prevent the output of sufficient amounts of blood to give rise to hypertension. Or, decrease in tone of the splanchnic vessels, due to either of the two mechanisms, might prevent the return flow to the heart to such a degree that high arterial pressure could not be maintained.

I noticed that the rate did increase in somewhat similar fashion to the increase observed by Heymans. One needs very badly to know also whether cardiac output changed, before deciding precisely what mechanisms are involved.

One would like to know, also, whether, under the circumstances under which hypertension does not occur, stimulation of the carotid sinus mechanism has the same effect as when nerves of the heart have not been operated upon.

There are some experiments of Barcroft that are of interest in this connection, too. One can imagine that the whole reaction, the whole development of hypertension, might take place in the first few beats of the heart. If the aorta is abruptly clamped, there is an immediate and sudden pressor response, which dies off gradually in the course of forty or fifty minutes. That rise in pressure can be completely inhibited if the return flow from the splanchnic region is cut off by clamping, at the same moment, the inferior vena cava. Suppose, then, that some change occurred in the heart or in the great veins to prevent increase in the return flow during the first few beats; the immediate large increase in pressure might never occur.

I should like very much to know whether Dr. Freeman has measured cardiac output, and whether he has tested the response to the carotid sinus mechanism.

Dr. Freeman (closing).—We have attempted to measure cardiac output with the ballistocardiograph of Dr. Starr and have observed in normal dogs that there is a marked increase in the force of ejection.

It is difficult to analyze exactly what happens after operations have been performed on the dog, but it does modify the reaction. I think that Dr. Steele has put his finger on the crucial point which is involved in consideration of this form of hypertension, and that is the question of the cardiac return, the return flow of blood to the right heart.

According to Starling's concept, the heart will put out whatever blood it receives, independent of the peripheral resistance, so that, with a given return of flow to the right heart, the pressure will vary directly with the peripheral resistance.

On the other hand, as the peripheral resistance is increased, unless the cardiac output is maintained constant, there will be a decrease in blood flow, because, as the resistance is increased, provided there is not a rise in blood pressure, the return flow will be diminished.

It seems to us that the failure to obtain hypertension in this experiment is probably ascribable to a deficiency in cardiac output. That is, the peripheral resistance increases but the return flow of blood to the heart is diminished.

I thank Dr. Steele very much for his discussion.

Discussion of the paper, "The Effect of Heparin in the Prevention of Thrombosis Experimentally Produced in Various Blood Vessels," by Dr. D. Y. Solandt, Dr. R. Nassim, and Dr. C. H. Best, Toronto, Canada.

Dr. Irvine H. Page, Indianapolis, Ind.—The results which Dr. Solandt, Dr. Nassim, and Dr. Best report leave no doubt about the effectiveness of heparin in preventing the thrombosis which is ordinarily produced by sodium ricinoleate. It is probably not too much to suppose that it will be equally effective in preventing thrombosis from other causes.

The method used for producing thrombosis is an interesting one. I should like to ask whether other, simpler, soaps also produce thrombosis. Dr. E. V. Allen and I (Arch. f. exper. Path. u. Pharmakol. **152**: 1, 1930) found that the ricinoleates were the most toxic of all the soaps we studied, that the highly unsaturated soaps were next, and that the saturated soaps were least toxic. Can you explain the mechanism of thrombus formation by soaps?

Obviously, a most important question is whether or not heparin can be employed therapeutically to arrest thrombus formation. Certain evidence indicates that it can, and Dr. Best and his associates can tell you of this better than I, because I know that they have been concerned in several of these attempts. It has gradually come to be realized that thrombi do not form instantaneously, so that there is time to arrest the process if it can be detected. That heparin can arrest it seems clear from the results we have just heard reported. Two problems immediately arise:

1. Is heparin the best anticoagulant for the purpose? 2. Can the diagnosis of early thrombus formation be made early enough? My belief is that heparin is, so far, the best, though by no means the cheapest, anticoagulant.

Synthetic substitutes for it may soon be found. Certainly a start has been made in the early diagnosis of coronary thrombosis. I need only cite Dr. Kerr's recent work. Since the work of Dr. Solandt, Dr. Nassim, and Dr. Best has done the important service of calling attention to the necessity of early diagnosis by placing a therapeutic tool in the hands of the physician, there will doubtless be a rapid advance in the efficiency of our diagnosis. The opening of new vistas in medicine, such as this, should give us pride in clinical investigation.

Dr. Arthur M. Master, New York, N. Y.—One cannot emphasize too much how important heparin may prove to be. We had occasion only yesterday to report that, in our post-mortem examinations of patients with coronary occlusion, almost half showed mural thrombosis and that embolism therefore was frequent. Perhaps heparin may prevent all this.

Another way of emphasizing the importance of the problem is to tell you that we now have a paper in press in which, with the help of board of health agencies, we have shown that at least half a million attacks of coronary occlusion take place yearly in this country.

Now, in regard to the premonitory symptoms, it has been reported that as high as 50 per cent of the patients do have premonitory symptoms. So, it may be possible to use heparin before occlusion has actually occurred. Certainly, it might be important to use heparin in those who suddenly develop a severe anginal syndrome due to coronary sclerosis.

I have not had any experience with the acetylcholine method of producing coronary thrombosis, so that the questions I raise are entirely theoretical. Dr. Solandt brought out that the mode of occlusion here is apparently different from that which takes place in man. In the latter, as you know, occlusion usually occurs as a result of intimal hemorrhage, whereas here it is really a clot formation on injured endothelium.

My last point is this: I wonder whether or not it would be worth while to take older dogs, who have, perhaps, coronary sclerosis, tie off a coronary artery, and then, after two days, or, perhaps better still, in the second week, give heparin and see whether it will prevent mural thrombosis and embolism.

Dr. John J. Sampson, San Francisco, Calif.—In confirmation of what Dr. Master has just stated, I wish to make a brief comment. Approximately two years ago, both Dr. Feil, of Cleveland, and Dr. M. Eliaser and I, in San Francisco, reported series of cases in which it was shown that in approximately 50 per cent of the cases of coronary artery occlusion the onset could be predicted by the occurrence of a certain, definite, premonitory symptom. This was persistent pain, which was not relieved by nitrites and was not followed by any of the recognized characteristics of acute coronary occlusion, such as, most particularly, the leucocytosis, increased erythrocyte sedimentation rate, or fever. There were no electrocardiographic changes in the majority of our cases.

It was felt, in discussing this syndrome with Dr. Feil recently, that perhaps these were instances of subintimal hemorrhage which later extended sufficiently to produce completely occlusive arterial thrombosis. Whether or not we can prove this pathologically remains to be demonstrated.

Dr. Chester M. Kurtz, Madison, Wis.—I think there is no question that heparin may now be regarded as a very potent drug in combatting thrombosis. However, there is one important precaution to be observed, namely, that one should carefully

differentiate between thrombosis and hemorrhage, particularly in cerebral accidents, before administering this preparation. In the presence of thrombosis, heparin is definitely indicated, but if one is dealing with hemorrhage, the condition may be aggravated rather than helped.

As has already been proposed by others, heparin may prove of value in the treatment of subacute bacterial endocarditis. There is reason to expect that some derivative of sulfanilamide will be developed which will have the power of destroying the *Streptococcus viridans* in the blood stream. If some drug such as heparin could be depended upon to inhibit or prevent the formation of the thrombotic vegetations on the heart valves which are known to protect and promote the growth of the organisms, there is a possibility that the infection might be overcome. Even if the heparin had to be given continuously over a period of time, it might prove of value and possibly provide another weapon against this disease which, at the present time, is fatal in practically 100 per cent of all cases.

Dr. Irving S. Wright, New York, N. Y.—We have had occasion to utilize heparin, and I should like to mention one experience which we had because I think it might be of interest to the audience as a whole.

This was in a patient with migratory thrombophlebitis, an individual who had had a fever for four or five months without amelioration from any form of therapy which we had been able to utilize, until we started with heparin.

We gave him heparin for twelve consecutive days intravenously, according to Dr. Best's own directions. During that time his temperature dropped to normal; in fact, it dropped to normal within six hours of starting the heparin and remained normal during the twelve days and for ten days thereafter.

After that period of time the temperature again began to show an irregular upward trend, which has persisted to date (many weeks). On the second attempt with heparin, about three weeks later, no effect whatever on the fever could be demonstrated.

There seemed to be no question that within a few hours of the original administration there was a heparin effect which persisted for the twelve days of administration and for ten days thereafter.

As noted, we were unable to repeat this experience, and I would like to hear Dr. Solandt's reaction on this matter.

Dr. Solandt (closing).—Putting the last first, I think it is a common experience that the fever caused by thrombophlebitis does very regularly drop quite soon after commencing the administration of heparin. We have no idea why this is so, because, as far as we have been able to discover, heparin has absolutely no effect on clots already formed. It prevents the further extension of the thrombus but has no effect on that already formed. I have no idea why the fever was dispelled in the first instance and was not affected in the second.

Coronary occlusion in old dogs will not, with any degree of certainty, bring about mural thrombus formation. We thought that it probably would, and we tested this idea in a number of old dogs by simply tying the coronary arteries. We obtained no mural thrombi.

I am very much interested to learn that so many physicians find useful premonitory signs associated with coronary thrombosis. The clear recognition of such signs will greatly facilitate the application of heparin to the treatment of this condition.

The cost of heparin is certainly a drawback to its use. At present, to heparinize a patient adequately about doubles the cost of hospitalization. In Canada it costs from four to seven dollars a day to keep the clotting time around twenty minutes. I believe that at present heparin is not made in the United States, so that you

would add 60 per cent to that figure. That possibly suggests a simple way by which you might reduce the cost of heparinization.

Discussion of the paper, "Activation of Renin and Its Vasoconstrictor Properties," by Dr. Kenneth G. Kohlstaedt, Dr. Irvine H. Page and Dr. O. M. Helmer, Indianapolis, Ind.

Dr. J. Murray Steele, New York, N. Y.—I can add very little to this really beautiful piece of work on a substance which has recently been investigated with increasing interest. Since the time of Tigerstedt and Bergmann, all of the work combined has served chiefly to show that renin can be quite regularly recovered from normal renal tissue. It has also been purified to a much greater extent.

But the discovery that it was not simply a single, simple substance, apparently manufactured by the kidney, with a direct constricting action on the peripheral arterioles, has revolutionized our thinking about the matter. We no longer think in such simple terms. We have to consider enzyme systems; we have to consider the possibility that two substances may have to combine in order to act. The possibility also exists that the absence of a substance which normally counteracts the action of renin must be considered. But, at any rate, it has distinctly changed our whole manner of thinking about renin.

It seems almost impossible that such a very potent substance can be present in normal renal tissue in much larger amounts without having a certain significance. One may think of it as supplying a long-range regulation of blood pressure, for it is not likely that pressure is ordinarily maintained by stimulation of the sympathetic nerves or by the constant inflow of adrenalin.

Perhaps such a substance that acts a little more slowly, whose action is a little more persistent and so well distributed over the whole arterial musculature, is the basis, the background, for the regulation of normal blood pressure upon which regulation by nervous mechanisms and adrenalin is superimposed.

It is at the moment difficult to link renin directly to hypertension, but this paper of Dr. Kohlstaedt, Dr. Page, and Dr. Helmer removes one more objection to doing so.

There are one or two questions I should like to ask. Have you attempted to inject plasma or purified renin separately in order to determine the time necessary for the two to react, that is to say, perfusing with serum present, then injecting a small amount of renin, and vice versa? How long after one is injected can you inject the other and obtain an effect? That might give some information as to the way these two parts of the whole interact.

I should like to congratulate Dr. Kohlstaedt, Dr. Page, and Dr. Helmer on this remarkable addition to our knowledge of renin.

Dr. Norman E. Freeman, Philadelphia, Pa.—Since the kidney has been identified by Goldblatt as the cause of the rise in blood pressure associated with clamping the renal artery, a series of different concepts has evolved.

First, there is the question of a pressor substance, which was not excreted. Then there is a pressor substance which is normally formed in the kidney and is normally excreted, but is not excreted when the renal artery is clamped. Recently, T. R. Harrison has suggested that normal kidney has an antipressor substance.

I think one of the most interesting and most suggestive concepts is the one which these investigators, Dr. Kohlstaedt, Dr. Helmer, and Dr. Page, have suggested today. We know that there is a substance, renin, present in the kidney, and the possibility that a coactivator is increased with disease of the kidney is, I think, extremely suggestive.

There is one question I would like to ask Dr. Kohlstaedt. He has mentioned vasoconstriction in the dog's tail. Studies on renin at other laboratories seem

to indicate that a rise in blood pressure is produced in an intact animal when renin is injected, but there is not a preferential vasoconstriction in the periphery. I wonder if Dr. Kohlstaedt can explain how he harmonizes this observation with his findings.

Dr. Alberto C. Taquini, Buenos Aires, Argentina.—We have found a pressor substance in the plasma of blood from an ischemic kidney, as in the experiments described. This was not present in normal plasma. When normal plasma is made of chemical substances, in order to separate the globulin and albumin, the pressor substance appears.

I am wondering if the renin dialysate, mixed with normal plasma, may produce these substances, which I feel are different from those liberated by the ischemic kidney.

Dr. Myron Prinzmetal, Los Angeles, Calif.—I wish to congratulate these workers on this very beautiful and important work. I should merely like to ask whether they have examined renal-vein blood of the ischemic kidneys of hypertensive animals to see whether the activator is present in increased quantities.

Also, I would like to point out that Dr. Ben Friedman and his co-workers have done similar experiments, but I think they came to the same conclusions. Friedman perfused an isolated dog's tail with plasma, plus renin, and obtained a constriction of the vessels of the tail, but when he perfused the tail with Ringer's solution, or with saline, he did not obtain any constriction at all.

Friedman's observations agree very well with those reported here today.

Dr. Louis N. Katz, Chicago, Ill.—I want to add my congratulations to those of the previous speakers. I think, for the first time, we have a way to explain why the substance first described by Tigerstedt and Bergmann might operate in the production of hypertension.

The results with renin are coming so fast from so many places that I think the question of priority nowadays, with modern transportation, radio, and, soon, television, need no longer concern us.

It is interesting that the observations just hinted at in this report, regarding the fact that renin is apparently not a sympathomimetic substance, we have been able to confirm in our laboratory.

I wish to know whether the authors have attempted to correlate this activator substance with the adrenal gland. They discussed the hypophysis, but there is still a controversy about the role of the adrenals. Is it possible that this coenzyme, or activator, or additive substance, comes from the adrenals?

Dr. Kohlstaedt (closing).—I wish to thank all the discussers. I will do my best to answer the questions, although some will be rather difficult because, as you all have seen, we have only begun our work. We feel that this method is still rather inadequate for close quantitative comparisons.

In answer to Dr. Steele's question, we have found that after long, repeated injections of renin, we were able to inject the plasma alone and produce vasoconstriction.

I am unable to explain fully Dr. Freeman's question. Vasoconstriction, which is not shown in the experiments, may be produced in parts of the body by renin.

In answer to Dr. Prinzmetal's question, the renal-vein blood has been studied, but we do not feel that we have carried on enough experiments to say that this blood contains less of the activator than the peripheral blood.

In answer to Dr. Katz' question, we have studied adrenalectomized animals, and find adrenalin present, but whether it is altered in quantity we are not certain.

Discussion of the paper, "The Effect of Deproteinated Pancreatic Extract in the Treatment of Intermittent Claudication in Arteriosclerotic Peripheral Vascular Disease (Intramuscular and Intravenous Administration)," by Dr. A. Wilbur Duryee and Dr. Martin Fisher, New York, N. Y.

Dr. Nelson Barker, Rochester, Minn.—Carefully controlled experiments by a number of different investigators have demonstrated that several different types of tissue extracts, when administered intramuscularly to human beings, exert an inhibiting effect upon the symptom of intermittent claudication. In general, this effect is inversely proportional to the degree of arterial insufficiency.

Unfortunately, we know relatively little concerning the exact constituent of these extracts which is responsible for the effect on intermittent claudication. It is an open question whether the present method of standardization of these extracts has anything to do with the anticlaudication factor. Efforts to demonstrate vasodilatation in human beings following intramuscular injection of pancreatic extract have failed, even though a definite inhibitory effect on intermittent claudication has been observed in the same individual during the same period.

It is possible that the factor in the extracts which inhibits intermittent claudication acts directly upon the muscle itself, or on the metabolism of the muscle, rather than indirectly through an increase in the flow of blood. In support of this concept is the observation that in a few cases of myasthenia gravis, intramuscular injections of tissue extracts have resulted in definite improvement of muscular strength and tone. Therefore, I think that there are definite objections to standardizing any of these preparations, including the deproteinated pancreatic extract, on the basis of inhibition of the vasoconstriction effect of epinephrine.

I should like to congratulate Dr. Duryee on his excellent, well-controlled experiment on a condition which does not readily permit of controlled experiments. At The Mayo Clinic we have used deproteinated pancreatic extract in a limited number of cases and, in general, our conclusions regarding its effectiveness are in agreement with those of Dr. Duryee.

One very obvious advantage of the aforementioned extract over other tissue extracts which have been used in the treatment of intermittent claudication is the fact that it does not produce pain at the site of injection. A second obvious advantage, as Dr. Duryee said, is the fact that the removal of the protein from the extract apparently removes the danger of systemic reactions. It appears that deproteinated pancreatic extract has just as good an effect on intermittent claudication as any of the other tissue extracts, and that it therefore represents an advance in this type of therapy.

Dr. Joseph B. Wolffe, Philadelphia, Pa.—The interesting work presented by Drs. Duryee and Fisher will aid greatly in determining the therapeutic value of pancreatic extract.

In 1929, when we first published a paper on the therapeutic application of an extract prepared from the pancreas, we were of the impression that extracts of all tissues had similar effects, and suggested the name "Tissue Extract," which we have used in subsequent publications. Further studies revealed that whereas similar extracts of various tissues have properties which are common to all, they also have properties which are specific for each particular tissue. In addition, it is also well to designate specifically the method of extraction, as well as the particular tissue employed, since different methods of preparation produce extracts with different properties.

The clinical employment of this particular type of pancreatic extract was suggested by the following observation: Dr. Vaquez, of Paris, noted that the stenocardia

of diabetic patients was greatly benefited when impure insulin was used. Thus, in addition to controlling the diabetes, he was able to relieve a great many of the patients of attacks of angina pectoris. When he used purified insulin, he found that not only did he fail to relieve painful cardiac failure, but that a great number of the patients developed anginoid attacks while under treatment.

Impressed by these observations, I felt that there must be an important by-product which was being discarded during the manufacture of insulin. With the aid of Sharp and Dohme's chemists and pharmacologists, we were able to prepare a fairly potent and moderately well-standardized preparation which we called "Tissue Extract No. 568." In this insulin-free pancreatic extract we found one fraction which has hormonal qualities, is parasympathicotropic, neutralizes epinephrine, and, whether alone or in combination with another fraction, influences lipoid metabolism.

Time will not permit me to mention many other pharmacologic properties which this extract possesses. We believe that the therapeutic value of pancreatic extract is the result of its influence on fat metabolism and its ability to neutralize epinephrine. We have also shown (at the Physiological Congress in Rome, in 1932, and again in Leningrad, in 1935) that if this substance is administered for a long period of time the blood-fat level falls. The deproteinized pancreatic extract which Dr. Duryee is using is simply Tissue Extract No. 568 in slightly purified form.

Judging from our studies, the best results obtained with this particular pancreatic extract (desympatone) are in cases of atheromatosis. Whether the lesions predominate in the vessels of the lower extremities, the coronaries, the aorta, the brain, or the kidneys makes very little difference. We look upon atheromatosis as a sequela of disturbed lipoid metabolism, most commonly secondary either to hepatic or pancreatic disease. Therefore, whether we are dealing with intermittent claudication, angina pectoris, visual disturbances, transitory hemiplegias, or any other symptom caused by an impairment of the circulation, if it is caused by atheromatosis we would expect to benefit the patient by administering this pancreatic extract, since by so doing we are attacking the underlying etiologic factor.

It is important to bear in mind that the preparations on the market are not as yet standardized carefully enough. Etiologic factors should be considered carefully, and pancreatic extract should not be used indiscriminately in all circulatory disturbances. Improper employment of the substance may lead to seemingly contradictory results and discourage investigators from studying this important subject.

We are at present investigating the effects of various fractions of pancreatic extract and have been fortunate in enlisting the cooperation of members of the Biochemical Division of the Franklin Institute. I feel certain that a very important substance will be isolated which will aid greatly in the prevention and treatment of atheromatosis.

Drs. Duryee and Fisher should be congratulated on their continued efforts in the application of a new remedy.

Dr. Duryee (closing).—I want to thank Dr. Barker and Dr. Wolffe for their excellent discussion of this subject. We realize only too well that the real action of this substance or substances (there is probably more than one in these extracts) is not known, and we are hoping that the next two years will see a considerable amount of work done in various research centers on this subject, so that perhaps we may obtain a substance that can be easily and readily standardized, such as insulin.

Discussion of the paper, "Effect of Estrogenic Substances Upon Vasomotor Instability in Human Extremities," by Dr. Louis G. Herrmann, Cincinnati, Ohio.

Dr. Kenneth Thompson, New Haven, Conn.—I feel somewhat apologetic in discussing Dr. Herrmann's paper, since he has had such wide experience in these matters, whereas I have only recently begun to study the peripheral vessels.

Having devoted the last five years to a study of endocrine glands, perhaps I can make a few suggestions in regard to therapy. I think the first thing to decide is whether the endocrine therapy is directed toward the primary cause of the malady or toward symptomatic relief.

I think that almost every endocrinologist would agree that the estrogens or other sex hormones probably have some effect upon the peripheral vessels, especially those of the skin. There is a good deal of evidence from various sources to support this statement, as illustrated by the following observations: the blushing of the newborn infant is thought to be caused by the extremely high estrogen content of the mother's and baby's blood at the time of birth; it has been demonstrated recently that the skin of eunuchoid men has a greater circulation of blood following androgen therapy; likewise, I think reliable experiments have demonstrated that the peripheral circulation is increased with estrogenic therapy.

Dr. Herrmann's main point, I believe, is that with estrogen therapy his patients with peripheral vasospasm have found benefit. I think the facts he presented are sufficient to warrant a further study of this form of therapy. These investigations, I think, should be carefully controlled with observations of the endocrine glands as well as of the peripheral vascular system. For instance, in the case of women we are able, by means of the endometrial biopsy, to obtain a fairly accurate estimate of exactly what activity is going on in the uterus and in the ovaries. We can tell whether the patient ovulates and produces a corpus luteum, or whether she doesn't. Whether the corpus luteum was acting in concert with the estrogens in Dr. Herrmann's experiments we do not know. Such endometrial studies should be carried out in his patients, in addition to the carefully controlled studies of the peripheral circulation.

I have not treated any patients with estrogens, but I have treated some with the androgen, testosterone propionate. I became interested in it because, two years ago, I started treating a eunuchoid man of twenty-eight with testosterone, and in the course of a year found that his calf muscles began to hypertrophy. At about that time I was also working in the peripheral vascular clinic, and found that some of my patients were elderly men with claudication and cold feet, and that they also were impotent. Their impotence was of four, or five, or six years' duration. Treatment of four of those patients, upon whom I could obtain reliable, constant-room-temperature studies, with oscillometric measurements, has brought about remarkable subjective and objective improvement.

I think that in those particular cases the deficiency is perhaps primarily in the hormone which has some important primary effect upon the blood supply of muscle and skin. I am not so sure whether such may be the case in these other types of peripheral vasospasm under discussion today. I do not think any of these questions can be settled until we carry out more studies of the type that have been proposed today.

Dr. Irving S. Wright, New York, N. Y.—I should like to remind Dr. Herrmann that we are always interested in knowing what other treatment the individual is subjected to at the time that experimental therapeutics are being undertaken.

One of the most difficult problems we have in the field of the peripheral circulation is the evaluation of any form of therapy. When individuals are put on a regime which includes abstinence from smoking, are given hot baths, and when their

whole environmental temperature is changed by wearing heavier clothes and warm socks, it sometimes greatly confuses the issue.

Therefore, we always have to take these factors into consideration. I should like to hear from Dr. Herrmann how they were controlled in this series of cases.

Discussion of the paper, "The Use and Value of the Vasoscillator in Diseases of the Peripheral Arteries," by Dr. C. E. Sanders, Kansas City, Kan.

Dr. Samuel H. Sedwitz, Youngstown, Ohio.—We all know about the Buerger-Allen exercises in the treatment of peripheral vascular diseases, and of various appliances made to help change the position of the leg and avoid muscular fatigue and tiring of the patient.

Years ago I had a railroad worker who devised a scheme of placing his leg in a hammock, suspended on a pulley, with counterweight, and at the same time saved himself the trouble of actually lifting the leg. I believe Dr. de Takats started the combined use of elevation of the leg and intermittent venous occlusion. Many men in Europe employ the same methods.

With respect to this oscillating bed, one has to employ it only a short while to appreciate the valuable contribution that Dr. Sanders has made in the therapy of the peripheral vascular diseases. In combination with intermittent venous occlusion, especially, one finds that it saves the trouble of shifting patients from their beds to receive the various other treatments, and when suction-pressure treatment is indicated, one can apply the boot when the bed is level and keep it level, especially when the treatment is applied for only a few hours.

Furthermore, in our clinic we have not only been using a heat cradle with thermostatic control (100° F.), but also, to conserve this heat, and prevent the loss which occurs when the bed pan is used or blankets lifted, we cover the involved extremities with a layer of paraffin which is wrapped up in an oilskin bandage. Since adopting this procedure we have noticed that the patients were relieved of their claudication and rest pain much more quickly.

Furthermore, not only has this bed proved satisfactory in our hands for the treatment of peripheral vascular diseases, but we have used it in cases of osteoporosis, nonunion of fractures, arthritis, and postoperative thrombophlebitis.

One particularly outstanding case was that of a man who sustained twenty-two fractures in various parts of the body—ribs, clavicle, scapula, both arms, pelvis, both femurs—and had no union at the end of nine and one-half months; in fact, he was about to receive roentgentherapy for parathyroid disease. After seven weeks' continuous treatment with this bed (he had not been able to move, and could hardly turn to bathe properly) he is back at his work as superintendent in a steel mill. He is walking perfectly except for a partial ankylosis of his ankle, which is aided by a brace.

Furthermore, in cases of Buerger's disease in which suction-pressure treatment provoked more vasospasm, we found that the oscillating bed would sometimes relieve the pain within forty-eight hours, whereas formerly, when we used only intermittent venous occlusion, if the symptoms were mild and the patient stopped smoking entirely, we succeeded occasionally in relieving the pain within 4 to 7 days. Invariably, these patients feel better, sleep better, eat better, and will cooperate more.

In the old arteriosclerotic cases, in which there are rest pain and claudication, the bed has proved very satisfactory, because the patient rests and the work of his heart is reduced to a minimum. When they are tired, or if the noise of the motor disturbs them somewhat, they touch the button and leave it off. They are easily fed and cared for generally. In cases of embolic occlusion, of which we

have had eight, the results have been satisfactory, with loss of pain due to vasospasm, and no local morbidity except in one case. Of course, about 50 per cent of these patients would have recovered spontaneously, without any resulting gangrene or permanent disability. When we would ordinarily give papaverine intravenously every four to six hours for two or three days, for relief of pain, only one to three doses were required when the bed was used. The legs would get warm within six to twenty-four hours. In one instance the patient had emboli at both iliac bifurcations; both legs were involved, but he lost only one (left), below the knee. This is the only patient who did not respond.

As was stated in a previous paper, shifting a patient with thrombophlebitis was helpful. We use the bed and find it most beneficial. The edema disappears sooner, i.e., in a week or ten days.

The chief advantage of the bed is that it enables us to improve the patient's peripheral circulation without any effort on his part.

Dr. Nelson Barker, Rochester, Minn.—At the Mayo Clinic we have been using oscillating beds in the treatment of occlusive peripheral arterial disease for three and a half years. Our experience with this type of treatment, based on results in eighty-eight cases, can be summarized as follows: There seems to be little difference in its effect on the various types of peripheral arterial disease when there are essentially the same degree of arterial insufficiency and the same type of pain. We have observed little or no effect on intermittent claudication. The most striking effect has been the relief of pretrophic pain, of the pain of ischemic neuritis, and of the pain caused by ulceration and gangrene. This relief of pain is not necessarily maintained when treatment with the bed is stopped. Skin temperature tests have showed that treatment with the vasoscillator usually produces some vasodilatation, but that this is usually not complete. There is also some increase in oscillometric readings after a period of continuous treatment, although this is not striking.

In summarizing the effects of treatment on seventy-two patients with rest or pretrophic pain, pain of ischemic neuritis, and pain caused by ulceration and gangrene, it was found that twenty-four, or 33.3 per cent, secured persistent, good results (relief of pain and healing of the gangrenous lesions). These patients were treated by means of the bed only. Persistent, good results also were obtained in eighteen other cases, although in these cases other types of treatment were given simultaneously and may have been responsible for the improvement. No persistent benefit was obtained in thirty, or 41.7 per cent, of the seventy-two cases, regardless of whether the bed was used alone or in conjunction with other types of treatment. It has been our experience that treatment with the bed has given better results than treatment with pressure and suction or with intermittent venous compression. The advantages of the bed appear to be that the treatment can be continued over long periods of time without interruption, and that it can be combined with various vasodilating procedures without the use of any constriction or pressure to the legs and without effort on the part of the patient. We have found it necessary to vary the position of the bed and time of the cycle to adapt it to the individual patient. We have seen only one untoward result during treatment; the patient had a severe infection of the foot, associated with extensive gangrene, as the result of thromboangiitis obliterans. In this case, ascending lymphangitis and lymphadenitis developed. There is some question whether the treatment with the bed was in any way responsible for this.

In conclusion, I wish to say that, in my opinion, the oscillating bed is a definite contribution to the treatment of peripheral vascular disease. I do not believe that this treatment should supplant other methods of therapy, but, in many cases, particularly in the presence of severe pain which is difficult to control, it is a valuable addition to other types of therapy.

Discussion of the papers, "A Review of Success and Failure in the Treatment of Vasospasm by Sympathectomy," by Dr. Alfred W. Adson and Dr. Bayard T. Horton, Rochester, Minn., and "Immediate Effects and Late Results of Sympathetic Denervation of the Upper Extremity by Pre-Ganglionic Section," by Dr. Reginald H. Smithwick, Boston, Mass.

Dr. Ashley Oughterson, New Haven, Conn.—It is very stimulating to hear reports from these two clinics, the Massachusetts General Hospital and the Mayo Clinic, in which so much has been done to forward the study of vascular disease. The experience of Dr. Adson, Dr. Smithwick, and others demonstrates that sympathetic denervation is effective when indicated.

I am afraid that anything I might add to the discussion of the operation on the upper extremity would add more confusion. We tried at first to make the operation as complete as possible, but some of the patients whose upper extremities had been operated on had a return of symptoms. After learning of the work of Dr. White and Dr. Smithwick, of the Boston group, we tried their operation, but we have not been able to make it uniformly successful, although it is better than the old procedure. This may have been due to differences in technique.

The syndrome of Raynaud's disease varies greatly; in some of the cases there is a pronounced emotional factor, whereas in others the symptoms are brought on by cold. Both factors may be present. It is our impression that in cases in which the emotional element is prominent we have had much more difficulty in getting a satisfactory result. We have seen that vasospasm may have a number of causes. It may be affected by a humoral mechanism or by the sympathetic nerves. As I have mentioned, there is evidence that Raynaud's syndrome frequently involves both. I think that in the future the work will probably evolve in such a manner as to indicate which of the operations may be eventually most effective.

I should prefer to say a few words about the general aspects of sympathectomy. As Dr. Adson has pointed out, it has now been in use more than fifteen years. When the operation was first introduced there were great hopes that it would be effective in relieving many symptoms of vascular disease. Those hopes, to some extent, have been fulfilled.

Sympathectomy is an operation of election, and, as is common with all operations of election, it should involve no risk to the patient and should leave the patient with no undesirable sequelae. The retroperitoneal approach for lumbar sympathectomy has made this operation relatively simple, and has eliminated the risk of the transperitoneal abdominal operation. Sympathetic denervation of the upper extremity was formerly followed by Horner's syndrome. As Dr. Adson pointed out, that is not necessary, even though we carry out an extensive operation in contradistinction to the one which seems indicated by the work of White and Smithwick. Thus, in the upper extremity, likewise, there are few undesirable sequelae.

The simplicity of the operation on the lower extremity, as contrasted with the upper, is considerable. This has encouraged us to use the operation more often on the lower extremities than we did formerly, that is, in more and more cases in which there was organic vascular occlusion, but in which a definite vasospastic element could also be demonstrated. Even though the blood flow may not be greatly increased, sympathectomy has the advantage that the effect is constant. Sympathectomy is also a most effective means of increasing the blood flow in a paralyzed limb. This has been sometimes overlooked, because we find orthopedic surgeons still trying to shorten the normal limb in cases of poliomyelitis. Children who have cold, sweaty extremities in which the circulation has not developed because of lack of muscular development may have their extremities lengthened if the operation is done before the epiphyses have united.

Histologic study has not demonstrated that the sympathetic nerves or ganglia are involved in any vasospastic phenomenon. Sympathectomy is therefore not directed at the etiology of the disease, and it is to be hoped that future investigation may provide a more rational treatment of such conditions as Raynaud's syndrome. However, it is well demonstrated, in the meantime, that sympathetic denervation has established itself as an effective therapeutic procedure over the period of fifteen years during which it has been used and has fulfilled the criteria of an elective operation.

Dr. Norman E. Freeman, Philadelphia, Pa.—Failures in the attempt to relieve vasospasm by sympathectomy have been associated with two processes which constitute real, major problems. One is that of sensitization by denervation. By this we mean that smooth muscle which has been robbed of its natural innervation becomes more sensitive to circulating hormones. Sensitization is much more effective after the postganglionic section which Dr. Adson and Dr. Smithwick have described.

The operations suggested by Dr. Smithwick and Dr. White, and described by Dr. Adson, have done much to avoid postganglionic denervation.

We are now confronted with the second major obstacle to successful surgical treatment, and that is regeneration. Whether it is regeneration, or whether it is the taking over of function by pathways which were already present, though dormant, may be a question in certain cases. Probably the latter will occur after incomplete operation, with recurrence of symptoms shortly after sympathectomy. The former is indicated by recurrence some months after the operation. Just how regeneration occurs is difficult to say. Preganglionic fibers will grow through muscle. They will grow through long stretches of tissue. If the ganglia are removed, it is difficult to see how the preganglionic fibers can come into contact with the heart muscle except through the agency of postganglionic neurons. Yet all of the postganglionic neurons have been removed by resection of the paravertebral ganglia. In spite of all this, inside of three or four months we have definite evidence of the resumption of control, sympathetic control, over the heart, in the experimental animal.

I think the problem of regeneration of sympathetic fibers is a major one, and not until we understand this fully can successful surgical treatment be assured.

Dr. Adson (closing).—I never take part in a controversial subject without being reminded of that play known as *Abie's Irish Rose.* After the couple was married, the priest and the rabbi concluded that there really was no material difference in their religion, since their respective groups expected to reach Heaven, although by different routes.

Discussions of this sort are extremely valuable, since they emphasize various phases of the subject. Although my views concerning the operative technique of sympathectomy for Raynaud's disease differ from those of Dr. Smithwick, I do want to emphasize the fact that such opinions are the result of observations, not of any personal animosity.

In the first place, we all agree that extensive lumbar ganglionectomy, whether done by the Royal, Pearl, Diaz, or the transperitoneal technique, results in dilatation of the peripheral vessels of the lower extremities. Though some hold that the vasodilating effect is caused by a preganglionic section of the sympathetic nerves, I am still of the opinion that the result is due to a thorough section of vasomotor fibers, whether the section is preganglionic or postganglionic. Removal of the fourth lumbar sympathetic ganglion, together with the first and second lumbar ganglia and the intervening trunk, is a combination of preganglionic and postganglionic section of the vasomotor fibers supplying the peripheral blood vessels of the lower extremities. Diaz's results were equally as good as those we have

obtained by resection of the second, third, and fourth lumbar ganglia and intervening trunk, although his procedure included the first and second sacral sympathetic ganglia, as well as the lumbar ganglia that we included. His procedure would naturally have to be considered as postganglionic section of the sympathetic fibers.

In reviewing the results we obtained by employing the Smithwick technique in the treatment of Raynaud's disease of the hands, we observed that changes in color would take place on exposing the hands to low temperatures. This, we think, was the result of leaving the vasomotor fibers intact, the explanation of which we believe is the fact that certain vasomotor fibers pass from the first thoracic nerve through the stellate ganglion to the brachial plexus. We further question the conception that the effectiveness of trunk resection of the third thoracic ganglion and division of the rami of the first and second thoracic nerve is greater than that of thorough resection of the lower cervical and first thoracic sympathetic ganglia, with removal of the sympathetic trunk in connection with ramisectomy of the eighth cervical and first thoracic nerves, a procedure which interrupts all sympathetic fibers that may enter the brachial plexus from lower thoracic ganglia. Many of our patients have had no recurrent symptoms during intervals of ten years. The work of Allen, Fathering, and Adson on sensitivity to epinephrine showed that although there was an increase in sensitivity to this drug following sympathectomy, there was no material difference in the reaction depending on whether the patient had been operated on by the Smithwick or Adson technique.

There is a possibility, as Freeman has stated, that regeneration may take place. However, the results of my study of experimental nerve regeneration indicated that if a gap of 2 cm. were permitted to exist between the severed ends of nerve fibers regeneration would rarely take place. This suggests that recurrences are more likely referable to the action of vasomotor fibers that have been overlooked at the time of operation. These fibers may have been injured sufficiently during the operation to account for their temporary dysfunction, but, as function became re-established, recurrent symptoms appeared.

Diseases resulting from spasm of the peripheral arteries of the fingers and hand occur sufficiently often to warrant further investigation, and it is my hope that some simple procedure may be developed to relieve the symptoms of this spasm. You may all be assured that I will employ the procedure if it is effective, regardless of who devised it.

Department of Reviews and Abstracts

Selected Abstracts

Thiele, G.: The Reactivity of Blood Pressure to Adrenaline in the First Years of Life. Ztschr. f. Kreislaufforsch. 31: 137, 1939.

This study was carried out on thirty-five young dogs. The blood pressure rise with maximum doses of adrenalin is slight at birth, and increases rapidly to reach adult magnitude at four months.

KATZ.

Osterwald, H.: The Action of Strophanthin in Experimental Coronary Insufficiency. Ztschr. f. Kreislaufforsch. 31: 225, 1939.

Eleven anesthetized dogs were used, and the flow in the left descending coronary artery was determined as well as that of the left pulmonary artery of left pulmonary vein by means of Rein stromuhrs, together with arterial and venous blood pressure.

He found that the coronary insufficiency produced by pituitrin, chloroform, or by ligation of the left descending coronary artery was improved by strophanthin, in that pulmonary flow and coronary flow increased.

KATZ.

Mönks, L.: Experimental Studies of Tonogenic Cardiac Dilatation Following Increased Venous Return. Ztschr. f. Kreislaufforsch. 31: 191, 1939.

Ten surviving rabbits' hearts were used, and it was found that infusion of saline into superior vena cava caused dilations of right auricle, elongation of right ventricle and rotation of heart on its long axis toward the left. Infusion into the pulmonary vein had its primary effect on the left auricle and ventricle with rotation to the right.

When a patent foramen ovale was present, both chambers were found to share the dilatation regardless of where the infusion was made.

These volume changes were reversible.

KATZ.

Gilligan, D. Rourke, Altschule, Mark D., and Linenthal, Arthur J.: Effects on the Cardiovascular System of Man of Fluids Administered Intravenously. Arch. Int. Med. 64: 505, 1939.

The effect of the intravenous administration of 1,000 to 1,500 c.c. of physiologic solution of sodium chloride on the glomerular filtration rate, as measured relatively by the urea clearance, of adults with normal renal and cardiovascular functions, has been studied. The fluids were injected at rates sufficiently rapid to cause increases in blood volume and cardiac output, decreases in plasma protein concentration, transitory increases in venous pressure and evidences of peripheral vasodilatation.

The glomerular filtration rate was not changed by the injections of fluid, even in those cases in which great changes in the systemic circulation were shown.

The absence of increase in glomerular filtration in the presence of hypervolemia, increased cardiac output, and lowered protein osmotic pressure, as induced in our studies, appears to result from specific adjustments in the renal vascular dynamics. No information is available from our studies as to the nature of such renal adjustments.

These results, together with those obtained by other investigators in certain clinical conditions and after the administration of certain drugs, demonstrate that the rate of glomerular filtration may not be affected in the presence of large changes in the systemic circulation.

AUTHORS.

Ogden, Eric, and Shock, N. W.: Voluntary Hypercirculation. Am. J. M. Sc. **198**: 329, 1939.

Two subjects are discussed; both of them are able voluntarily to accelerate their pulse rates at the word of command. This acceleration is accompanied by increased systolic and diastolic blood pressures, increased rate of respiration, ventilation volume, oxygen intake, and carbon dioxide output. The onset and disappearance are abrupt.

The quantitative consideration of the magnitude and time relations of these functions indicates that there is a true hyperventilation with excess elimination of carbon dioxide, a true increase in metabolism with excess oxygen utilization, and a hypercirculation, or circulation in excess of the metabolic requirement. Epinephrine might be responsible for the cardiac acceleration and the increased blood pressure, and, by discharge of blood reservoirs, for the increased circulation. But it is believed that the phenomenon appears and disappears so rapidly that epinephrine cannot be solely held to account. In the nine reports cited, covering some fifteen other cases of voluntary acceleration of the heart, there is no instance in which the acceleration was not accompanied by one or more of the other phenomena described.

AUTHORS.

Schleicher, I.: Acute Cardiac Damage in Healthy Individuals Following Athletics. Ztschr. f. Kreislaufforsch. **31**: 105, 1939.

Athletics can lead to cardiac damage in healthy subjects by causing trauma and commotio cordis, if excessive bodily exertion of long duration or of short, intense nature is carried out.

Following such heart damage death may occur, or myocardial infarction, chronic heart weakness, traumatic valvular defects, arrhythmias, and tachycardias may ensue. It would appear that infection, including focal infection and the so-called vagotonic disposition, may be considered a predisposing cause for the hazards.

Illustrative case reports are given, one of nonpenetrating chest wounds, six of long duration exertion, and two of severe exertion.

KATZ.

Schlomka, G., and Witsch, F.: The Evaluation of the Relative Duration of Systole. IV. In Obese People. Ztschr. f. Kreislaufforsch. **31**: 142, 1939.

The electrical systole is on the average relatively longer in obese than normals of the same age group. This is based on measurements on 200 obese people. This increase in systole seems related to the degree of left axis shift.

KATZ.

Roemheld, L.: Alterations of Cardiac Minute Volume by Diet. Ztschr. f. Kreislaufforsch. **31**: 73, 1939.

The author studied twenty patients and used Grollman's method for cardiac output. Normal persons and mild cardiacs showed an increase in cardiac minute output when the diet is increased by adding 1 to 1¼ liters of water or 6 to 10 grams sodium chloride daily to the regular diet. When the diet consists only of fruit or of salt-poor dry food, the minute volume output is decreased. Severe cardiacs, however, reacted in the exact reverse manner.

KATZ.

Evans, Courtenay: Changes in the Chest Lead Electrocardiogram in Coronary Thrombosis. Brit. Heart J. **1**: 161, 1939.

In the T_1 type of electrocardiogram after coronary thrombosis, the changes in Lead IV occur in the following sequence. The initial wave R disappears immediately in half the cases, and elevation of the R-T segment, 3 mm. above the isoelectric level, occurs at the same time in three-quarters of the cases. The T wave becomes inverted on the third or fourth day, synchronous with or slightly earlier than inversion of T_1, and sometimes many days earlier. At the same time, the R-T elevation diminishes, and, in half the cases, changes any time after the fourth day into a humped upward convexity with broad slurring of the curved portion. Return of RS-T to normal, with disappearance of the humping, occurs after several weeks. T-wave inversion disappears in half the cases between the third and sixth month, but in half the cases it persists. The initial wave R, when once absent, usually tends to remain absent; the initial complex in these cases sometimes becomes diphasic (QR).

In the T_3 type of electrocardiogram, RS-T is depressed 3 mm. below the isoelectric level, returning to normal within a few days in two-thirds of the cases. The initial R wave is present, the S wave is often small, and sometimes a W-shaped complex is seen. Later, humping of the S-T segment with a downward convexity occurs in a few cases, but is not common. The T wave is upright and tends to increase in amplitude; it may attain 13 to 19 mm. in the second or third week. As a rule the changes in Lead IV, after the initial RS-T depression has passed, are slight and not very helpful in diagnosis.

Post-mortem evidence suggests that T_1 and T_4 inversion, and absent R_4 with elevation of RS-T in Leads I, II, and IV, indicate an anterior infarction, and that T_2 and T_3 inversion with depression of R-T_4 indicates a posterior infarct. Where absence of R_4 and T_4 inversion is associated with inversion of T_2 and T_3, the evidence points to infarction of both anterior and posterior ventricular walls. The third type of occlusion, involving the left circumflex artery and causing left lateral infarction, shows RS-T depression in Leads I, II, and IV, with inversion of T in Leads I, II, and IV. These changes are often of a transitory nature and may be associated with auricular fibrillation.

AUTHOR.

Eliaser, Maurice, Jr., and Konigsberg, Jerome: Electrocardiographic Findings in Cases of Ventricular Aneurysm. Arch. Int. Med. **64**: 493, 1939.

There is an electrocardiographic syndrome, occurring in 27.3 per cent of cases of aneurysm of the left ventricle following occlusion of the coronary artery, which may be considered to be a presumptive sign of this lesion. It consists of a downward directed major deflection in Lead I, with inversion of the T wave and an upright P wave. The ventricular complex in Lead III is upright.

Another type, occurring in 36.4 per cent of cases, presents ventricular complexes directed downward in Leads II and III with an upright major deflection in Lead I that may or may not be of low amplitude.

In 18.2 per cent of cases of cardiac aneurysm, the electrocardiogram shows left bundle branch block, and there were a like number of various other equivocal records, which, although consistent with disease of the coronary artery, were not of diagnostic significance.

Roentgen examination, especially roentgenkymography, would seem to be the most reliable means of corroboration of the diagnosis of ventricular aneurysm and should be performed when one or the other of the two types of cardiogram observed in 63.7 per cent of all cases is obtained.

No correlation between the location of the aneurysm and the specific type of electrocardiogram obtained has been established.

The use of the Einthoven equilateral triangle is a convenient means of visualizing deviation of the axis. However, other more recent theories must be considered in order to explain the two divergent types of cardiogram obtained with pathologically identical lesions.

AUTHORS.

Radványi, Géza: Electrocardiographic Prognosis. Ztschr. f. Kreilaufforsch. 31: 83, 1939.

The author analyzed a follow-up study on forty-nine cases with intraventricular block or inverted T_1 or $T_{1,2}$ and found that the outlook is not as serious as formerly thought. It is not the electrocardiogram but the underlying disease that determines the prognosis.

KATZ.

Graf, L.: The Electrocardiogram in Single and Double Ovum Twins. Ztschr. f. Kreislaufforsch. 31: 337, 1939.

There is a much greater similarity in electrocardiograms in single ovum twins than in double ovum twins. Cases of mirror image QRS complexes are described in the former type of twins. The study is based on twenty-four of the first, and fourteen of the second type of twins.

KATZ.

Schlomka, G., and Cramer, H.: Sinus Arrhythmia in Presence of Extrasystoles. Ztschr. f. Kreislaufforsch. 31: 240, 1939.

It was found that in the presence of extrasystoles, sinus arrhythmia was more noticeable than in their absence.

KATZ.

Marx, L.: The Q-T Interval Following Extrasystoles. Ztschr. f. Kreislaufforsch. 31: 42, 1939.

The author analyzed fifty instances of postextrasystolic beats and found that the Q-T interval was shorter than anticipated from Fridericia's formula relating electrical systole to cycle length, and this relative shortening was greater, the greater the compensatory pause. The author interprets this to indicate that large stroke volumes are the cause of this abbreviation of systoles.

KATZ.

Schlomka, G., and Dressen, M.: Physiological Irregularities of the Heart Beat. XI. Respiratory Variations of Q_3. Ztschr. f. Kreislaufforsch. 31: 46, 1939.

Respiratory variations in Q_3 occur in normal subjects as well as in cardiacs. Usually this consists of an inspiratory decrease, occasionally an inspiratory increase in the size of the wave. The decrease in Q_3 with inspiration seems most marked in those cases with the most marked sinus arrhythmia.

KATZ.

Spang, K., and Korth, C.: The Electrocardiogram in Hyperthyroidism. Arch. f. Kreislaufforsch. 4: 189, 1939.

This is a monograph of about 130 pages in which the literature has been thoroughly studied. The author discusses arrhythmias, contour, and the effect of medication. This study includes two hundred cases of their own. While all sorts of changes are seen, the authors emphasize the development of a depressed S-T and an inversion of the T wave as evidence of acute increase in the thyrotoxic state. They also point out frequency of tall P_2 and consider this evidence of stasis in the lesser circuit since as condition improves, P gets smaller and the curve shows a shift to the left.

Digitalis has little effect on heart rate in thyrotoxicosis, but an exaggerated ability to produce the digitalis T wave. This is considered of value diagnostically. Other details must be sought for in the original article.

KATZ.

Manning, G. W., McEarchern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches. Arch. Int. Med. 64: 661, 1939.

The mortality following sudden occlusion of the anterior descending branch of the left coronary artery in the anesthetized dog is less than 10 per cent. For the conscious dog the mortality is about 40 per cent.

For sudden occlusion of the left circumflex branch, the mortality is about 25 per cent with anesthesia and about 75 per cent without.

The great increase in mortality for the conscious animal may be the result of a reflex spasm of collateral arterioles and small arteries producing additional areas of ischemia.

All the animals that died suddenly after ligation in the conscious state showed evidence of ventricular extrasystoles, tachycardia, and fibrillation in that sequence.

AUTHORS.

Master, A. M., Dack, Simon, and Jaffe, H. L.: Age, Sex, and Hypertension in Myocardial Infarction Due to Coronary Occlusion. Arch. Int. Med. 64: 767, 1939.

The influence of age, sex, and hypertension on the incidence, clinical course, and prognosis of coronary occlusion has been analyzed in 500 consecutive cases.

Approximately two-thirds of the attacks occurred between the ages of 45 and 65, and almost one-third before 50 years. The peak occurred in the sixth decade.

The number of initial attacks rose progressively until the age of 45 years; then a level was maintained until the age of 64, after which there was a rapid decrease. However, when the number of attacks was correlated with the census

of the general population in each age group, there was a progressive rise in the incidence of attacks with advancing age to 74 years.

Particular attention was paid to a group of 39 patients aged 27 to 39 years. The susceptibility of these young persons to coronary sclerosis and occlusion could not be attributed to rheumatic fever, syphilis, diabetes, hypertension, or a familial or hereditary trait.

The mortality rate varied with age, increasing gradually until the age of 59 and rising sharply in the older age groups. Coronary occlusion is rarely fatal before the age of 40, since the occlusive process is often localized to one artery and the myocardium is not diffusely damaged.

The frequency of multiple attacks was the same in all age groups. Young and old persons are equally susceptible to subsequent attacks of coronary occlusion after an initial attack.

The commonest cause of death before the age of 50 was arterial embolism; after 50, it was cardiac failure.

The ratio of men to women was only 3.4:1. The average age of the women was higher than that of the men, and the incidence in women below the age of 40 was relatively small.

Diabetes was frequent in women over 50 but uncommon in men below 70. In women the incidence rose sharply with increasing age.

Cardiac enlargement and heart failure increased with age, being uncommon in the young. They were more common in women than in men. Pulmonary edema with little or no pain not infrequently initiated an attack, particularly in women.

Hypertension occurred in more than half the men and in four-fifths of the women. The incidence rose with age from 36 per cent in the fourth decade to 74 per cent in the seventh decade. There was no effect on the mortality rate.

Hypertension is an etiological factor in coronary occlusion, for its incidence in this series was definitely greater than that calculated for the general population. Furthermore, the ratio of attacks per unit of the hypertensive male population was five to eight times as great as that for patients with normal blood pressure, although both ratios increased with age in the same proportion. Hypertension accelerates the aging process.

AUTHORS.

Maitra, J. M.: Coronary Occlusion. Medical Bureau 3: 185, 1938.

Notes from numerous cases of coronary thrombosis in native Indians are given, describing symptom of the sudden death, together with physical signs and electrocardiographic findings.

The author has found that in cases with chronic coronary occlusion with standard characteristics in electrocardiogram, the symptoms of external pain and discomfort may disappear completely after the use of hydrocyanic acid. He believes that fresh blood vessels develop throughout the myocardium and eventually form anastomoses. Several cases showing favorable results are recorded. There is a discussion of the anatomical explanation of symptoms and signs of coronary insufficiency.

MCCULLOCH.

Müller, Carl: Angina Pectoris in Hereditary Xanthomatosis. Arch. Int. Med. 64: 675, 1939.

Hereditary heart disease due to xanthomatosis is fairly common. It is believed to have been demonstrated as a dominant factor in seventeen families. Xanthomatosis gives rise to a special form of arteriosclerosis which is etiologically and,

consequently, clinically different from ordinary arteriosclerosis. It is possible that it may be different anatomically, too. Xanthomatous deposits may cause valvular lesions, but far more commonly the changes are in the coronary arteries, with angina pectoris. This may occur in young but more frequently in middle-aged and old persons. Symptomatically this form of angina pectoris does not differ from the usual form. In addition to chronic and long-continued heart disease, the condition may cause sudden death. Infarction of the myocardium is also a frequent result. Hypercholesteremia is present, most marked in connection with xanthoma tuberosum, but there is no definite relation between hypercholesteremia and xanthomatous deposits in the skin. Xanthomatous cardiac lesions probably may develop in persons who have no evidence of xanthomatosis in the skin. Xanthoma tuberosum and xanthelasma may be overlooked in clinical examinations and may be confused with other cutaneous conditions also. The occurrence of heart disease in families should direct the attention to xanthomatosis, especially when rheumatic fever, syphilis, or hypertension does not appear to play any role. In the cases here reported, hypertension was infrequent. Finally, it seems possible that causal and prophylactic treatment may prove to be of value.

AUTHOR.

Middleton, William S., and Burke, Mead: Streptococcus Viridans Endocarditis Lenta. A Clinico-Pathologic Analysis of the Experience in the Wisconsin General Hospital. Am. J. M. Sc. **198**: 301, 1939.

Certain details in this clinico-pathologic analysis of eighty-eight cases of *S. viridans* endocarditis lenta justify especial emphasis:

Further evidence is adduced to support the thesis of a close relationship between congenital and rheumatic lesions of the heart and endocarditis lenta.

Acute upper respiratory infections, rheumatic fever, infected abortion, dental extraction, and massage for nonspecific prostatitis apparently served as precipitating factors in the development of certain cases of this condition.

Contrary to the accepted opinion, congestive heart failure may attend or mask this condition.

The clinical manifestations and course of this affection are notoriously varied and inconstant. After the cardiac changes incident thereto, particular attention has been directed to its toxic and its embolic features. Splenic and renal changes, including embolism, were very frequent. Mycotic aneurysms offered serious diagnostic problems. Cerebral accidents were not infrequent. Occasionally a mycotic aneurysm of a cerebral vessel may explain certain neurologic phenomena of this condition. Again the clinical picture may suggest thyrotoxicosis, and the unexplained elevation of the basal metabolic rate may add to the diagnostic confusion.

This study offers material support to the importance of the diagnostic triad, i.e., petechiae, splenomegaly, and positive blood culture for the *S. viridans*. Given the background of a congenital or a rheumatic heart lesion and a remittent fever, this triad offers the logical direction of attack.

The prognosis of *S. viridans* endocarditis lenta is very grave. Only inferential evidence of the pace of the decline is offered by the circulatory, renal, embolic, toxic, constitutional, and hematologic reactions. Although remissions of varying durations and degrees are the rule, certain of these patients undergo a rapidly progressive decline. Attention has been directed to the ominous significance of the euphoria that attends late remissions.

This group included one instance of healed endocarditis lenta. The clinical activity apparently occurred at a period removed from the hospitalization. All therapy in the remaining number (87) was unavailing.

AUTHORS.

Crynes, S. F., and Hunter, Warren C.: Traumatic Rupture of the Pericardium. Arch. Int. Med. **64**: 719, 1939.

Traumatic rupture of the pericardium is not, as the literature indicates, a rare occurrence. It is no doubt encountered as frequently in every series of autopsies on persons dying as a result of trauma as it has been in this series.

Commonly, pericardial rupture is merely one of many injuries and in most instances contributes little or nothing to the cause of death. One may rightly anticipate therefore that few examples of long survival will ever be recorded.

The pertinent data in 22 cases found among 4,107 consecutive and unselected cases studied at autopsy have been tabulated and evaluated. Among these, 1 case stands out conspicuously, not only in this group, but among all others on record, because of the fact that the child survived for two and one-half years, and, further, because of the singular mechanism responsible for the sudden death. This case is described in detail.

The views of others and the authors as to the mechanical principles involved in the production of pericardial rupture are given.

AUTHORS.

Harris, Jerome S., and Farber, Sidney: Transposition of the Great Cardiac Vessels, With Special Reference to the Phylogenetic Theory of Spitzer. Arch. Path. **28**: 427, 1939.

In a review of the hypotheses concerning the pathogenesis of transposition of the great cardiac vessels, particular attention has been paid to the theories of Rokitansky and of Spitzer, since they represent the ontogenetic and phylogenetic aspects of this malformation. An attempt has been made to present in detail the essence of the theory of Spitzer as gathered from a study of all pertinent literature. Nineteen examples of transposition from the Infants' Hospital and the Children's Hospital collection have been analyzed in illustration of that theory. This series included examples of overriding aorta, complete transposition of the tricuspid valve, bulboventricular inversion, atresia of the tricuspid orifice, and cor biatriatum pseudotriloculare with mitral atresia. One case showed a very rare primitive arrangement of the chambers of the heart, while another showed the combination of fetal endocarditis and aortic transposition. Incidental malformations of the heart included various deformities of the interatrial and interventricular septums, valvular abnormalities, aortic coaretation, and a complete vascular circle around the trachea and esophagus.

In each case, particular attention was paid to the course of the main coronary arteries. Inversions, corrected transposition, and the relation of mitral atresia to transposition were briefly examined.

It may be concluded that the theory of Spitzer marks an important advance in the understanding of cardiac development and certain cardiac malformations. Although many data, accumulated from embryology, phylogeny, and teratology, tend to support the theory, further proof will be necessary before it can be accepted completely.

AUTHORS.

Robinson, Samuel C., and Brucer, Marshall: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons. Arch. Int. Med. **64**: 409, 1939.

A new and more rational range of normal blood pressure is postulated as the result of (1) a statistical study of 10,883 persons, (2) a study of five to ten year continuous records of 500 persons, and (3) an appraisal of mortality at

various pressure levels. The normal range of systolic blood pressure for men and women is from 90 to 120 mm. of mercury. The normal range of diastolic blood pressure for men and women is from 60 to 80 mm. of mercury. A normal person attains his mature blood pressure at about adolescence and keeps that range throughout life, except for a slight rise at about the twentieth year. Normal blood pressure does not rise with age. Prehypertensive and hypertensive pressures do rise with age.

"Hypotension" is neither a disease nor a disease entity; it is an ideal blood pressure level. In the absence of other findings this is true of pressures that occasionally dip to the level of 80 systolic and 50 diastolic. The commonly described symptoms of the disease called "hypotension" can be ascribed with equal statistical accuracy to any level of blood pressure.

Blood pressure should be considered a physiologic measurement in continual diurnal flux, highest during the afternoon, lowest during the early morning hours. The daily and yearly variation of normal blood pressure is from 5 to 10 mm. of mercury. Higher levels of blood pressure show proportionately greater and more erratic yearly variations. Lower levels of blood pressure show smaller and less erratic yearly variations. A blood pressure history is more nearly normal as it shows occasional pressures below 110 systolic and 70 diastolic. A person who has a history of pressures which occasionally dip to the 90 systolic and 60 diastolic level, or even to the upper part of the 80 to 90 systolic and 50 to 60 diastolic range, has an added assurance of not becoming hypertensive.

A blood pressure history of over 120 systolic and 80 diastolic over a ten year span in a man or woman is pathologic, and is an almost infallible sign of incipient hypertension. Once a pressure is definitely established in this range it seldom if ever will become normal. Transient elevations of blood pressure should not be ignored. They should be suspected of a further, more frequent, and possible permanent rise. Moderately high blood pressures are incipiently hypertensive. Persons with hypertensive heart disease are recruited from persons with incipiently hypertensive blood pressure levels. High blood pressures tend to become even higher, the higher pressures invariably resulting in hyperpiesia. High blood pressure is a long-term disease having its genesis at an early age. It is not a disease that suddenly emerges with middle age. Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive.

A study of any normal physiologic measurement must check with mortality data. One of the criteria for the selection of a normal range is that it be compatible with the lowest possible mortality and the longest life span. The mortality rate increases progressively with an increase in systolic or diastolic blood pressure. Persons with low blood pressures have the lowest mortality rate. Those with blood pressures persistently over 120 mm. of mercury systolic and 80 mm. diastolic have a higher mortality rate than those with blood pressures persistently under 120 mm. systolic and 80 mm. diastolic.

AUTHORS.

Rasmussen, Hakon, and Thingstad, Rolv: Cardiovascular Changes in Essential Hypertension With Special Reference to the Electrocardiogram in Hypertension. Acta med. Scandinav. **101**: 237, 1939.

A group of 100 patients with essential hypertension has been examined with regard to cardiovascular changes (cardiac function, size of heart, electrocardiogram, breadth of aorta, calcareous deposits in aorta and in the tibial arteries), and the findings have been more closely analyzed.

Only 8 per cent of the patients were without any pathologic findings (of varying import) in the cardiovascular system.

The height of the blood pressure was found independent of the degree of cardiac enlargement and electrocardiographic changes.

A study of the relationship between electrocardiogram and heart size brought forward some important points with a bearing on the pathogenesis of the electrocardiogram in hypertension and on the pathogenesis of the so-called "bundle branch electrocardiogram of commoner form," and the following conclusions were drawn:

Electrocardiograms of hypertensive patients are without any constraint grouped into four distinct types, characterized by varying alterations in the QRS deflection, S-T segment and T wave. The types seem to represent different stages of one and the same evolution. A closer examination of the relation between these four electrocardiographic types and the cardiac enlargement revealed a strong correlation between these types and the size of the heart. Thus the Types 1 and 2 with comparatively small changes in the electrocardiogram corresponded to slight and moderate enlargement of the hearts, while the patients with gross changes in electrocardiogram, Type 3 ("left ventricular preponderance curve") and Type 4 ("bundle branch block electrocardiogram of commoner form"), had the larger hearts.

The authors feel, therefore, that the electrocardiographic changes, above described as characteristic of the electrocardiogram of hypertension, are due to varying degrees of left ventricular enlargement (dilatation and/or hypertrophy), and not due to disease of the coronary arteries.

The bundle branch block electrocardiogram of commoner type (our Type 4) was observed in 7 of our 100 hypertensive patients. An analysis of the 7 cases together with another group of 21 cases with this electrocardiographic picture revealed that all 28 cases with "bundle branch block electrocardiogram of commoner form" were characterized by gross left ventricular enlargement. The chief cause of "bundle branch block electrocardiogram of commoner form" (classical terminology: right bundle branch block) is supposed to be severe left ventricular enlargement.

AUTHORS.

Thomas, Henry M., Jr.: Transient Paralysis From Postural Hypotension. Bull. Johns Hopkins Hosp. **65**: 329, 1939.

A case of recurring transient paralysis of the right arm and leg is reported. The attacks occurred when the patient was upright, and frequently soon after arising from a sitting or lying position. He was found to suffer from a moderate form of postural hypotension which, in conjunction with cerebral arteriosclerosis, offered an explanation for the mechanism of the attacks. When the patient was elevated on a mechanical tilting table the systolic blood pressure fell below 90 mm. of mercury and temporary paralysis of the right leg occurred. Most of the previously reported cases of recurrent transient paralysis of brief duration probably belong in the same group.

Momentary clouding of the vision in one eye occurred in some of the attacks and probably resulted from temporarily inadequate blood flow through the ophthalmic branch of the internal carotid artery of the central retinal artery.

Treatment designed to prevent excessive drops in blood pressure has greatly diminished the number and severity of the attacks.

AUTHOR.

Miller, H. R.: The Occurrence of Coronary Artery Thrombosis in Polycythemia Vera. Am. J. M. Sc. **198**: 323, 1939.

Although there have been extensive investigations on the principles underlying the mechanism of blood clotting and on the formation and organization of thrombi, we are still unable to explain the precipitating cause of an intravascular clot. Nowhere is this truer than in connection with the coronary arteries, and this problem assumes a fresh interest in connection with an analysis of coronary thrombosis in polycythemia when these vessels remain unaltered. The cases we have described illustrate that the clinical manifestations of thrombosis in a normal coronary vessel are indistinguishable from those observed in thrombosis of arteriosclerotic coronaries. These clinical features range from complete silence, e.g., few or no clinical signs at the time of the occurrence of the thrombosis as in some of our cases, to sudden and dramatic onset of shock, pain, and so on, as observed in our last case. The sequelae of disturbed cardiovascular hemodynamics and the evolution of anatomic alterations in the heart are not different for polycythemic patients who develop coronary thrombosis. Arteriosclerosis was absent, or at most minimal, in the coronary tributaries; in several instances, this complete or almost complete freedom of coronary sclerosis was in contrast to the general arteriosclerosis of other parts of the vascular system. The myocardial lesions were not limited to microscopic size but were gross and followed the occlusion of good-sized coronary vessels. The five cases in this series of seven polycythemics examined at autopsy suggest that the concurrence of polycythemia vera with coronary thrombosis or with marked myocardial damage of the type associated with coronary thrombosis, is more frequent than we were wont to believe and that coronary thrombosis, as well as other arterial and venous thromboses, is not to be dissociated from the pathogenesis of polycythemia vera.

It is of some interest to direct attention to the clinical seizures of precordial pain in polycythemic individuals in whom the coronary vessels are not occluded. The character and the mechanism of this manifestation may be akin to that observed, with and without intermittent claudication, in states of anemia. It has long been known that polycythemia or anemia may be responsible for many of the same clinical features and among them, we have reason to believe, precordial pain should be included.

AUTHOR.

Katzin, Herbert M., Waller, John V., and Blumgart, Herrman L.: "Cardiac Cirrhosis" of the Liver. Arch. Int. Med. **64**: 457, 1939.

An investigation of an unselected series of 2,000 consecutive cases in which autopsy was performed was undertaken in order to learn the incidence, types, and degrees of hepatic fibrosis in cases of congestive failure and to make a comparison of these findings with those in cases in which congestive failure was absent.

Of the 286 cases of chronic passive congestion, there was an increase of hepatic fibrous tissue in ninety-five, or 33 per cent. In 1,714 cases in which chronic passive congestion was absent the incidence of hepatic fibrosis was 12 per cent. The causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure. The incidence of each of the various kinds of fibrosis except biliary fibrosis was higher in 286 cases of congestive failure than in the remaining 1,714. The only type of increase in connective tissue peculiar to the cases of cardiac decompensation was central fibrosis, for, with a single exception, no instance of central fibrosis was found in 1,714 cases in which autopsy disclosed an absence of congestive failure. Of

particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with an incidence of 9 per cent in the 1,714 cases in which chronic passive congestion was absent. This suggests that chronic passive congestion with resulting anoxemia, by increasing the susceptibility of the hepatic tissue, is also a contributing factor to fibrosis in the portal areas.

By the evidence obtained in this investigation the meaning of the term "cardiac cirrhosis" is clarified. Cardiac cirrhosis signifying morphologic increase in connective tissue in the liver consequent to congestive failure is present in the majority of patients who have suffered from even mild congestive failure for nine months or more; the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, signifying extreme fibrosis which clearly results from chronic passive congestion and which causes evidences of portal obstruction, does occur, but is rare. Of the 286 cases of congestive failure, there were only fifteen in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure, and particularly the presence of a palpable spleen. Not infrequently, however, the liver may be enlarged. In such cases, although increased fibrous tissue is present and the surface of the liver is generally nontender and sometimes somewhat irregular, the dilatation of the sinusoids leads to an increase in the size of the liver. In a patient in whose case a clinical diagnosis of cardiac cirrhosis has been made, one may find portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

AUTHORS.

Rabb, W., and Schönbrunner, E.: The Tendency of the Electrocardiogram to Become Normal in Angina Pectoris Patients Whose Adrenals Have Been Irradiated. Arch. f. Kreislaufforsch. 4: 362, 1939.

Twenty-eight out of thirty-eight patients with angina pectoris were subjectively improved following one or more deep x-ray irradiations of the adrenal areas and were free of symptoms thereafter for eleven months on the average.

In ten out of thirteen patients showing an electrocardiogram of hypoxia (either at rest or during exercise), there was a tendency for the electrocardiogram to return to normal. The authors attribute these changes to irradiation therapy.

KATZ.

Edens, E.: Indirect and Direct Strophanthin Action. Ztschr. f. Kreislaufforsch. 31: 177, 1939.

Extrasystoles resulting from indirect strophanthin action are no ground for stopping drug when the heart's condition requires its use.

KATZ.

Book Reviews

ANGINA PECTORIS: NERVE PATHWAYS, PHYSIOLOGY, SYMPTOMATOLOGY, AND TREATMENT. By Heyman R. Miller, M.D., Attending Physician, Sydenham Hospital, Associate Attending Physician, Montefiore Hospital, New York. Baltimore, 1939, 275 pages, 39 illustrations, $3.25, The Williams and Wilkins Company.

This book contains chapters on the clinical features of anginal pain, the anatomic arrangement of the nerves which transmit it, and the physiologic and psychologic theories which have been evolved to explain the production of the attacks and the variable intensity of their reception in the sensorium. A quarter of the book is devoted to the medical and surgical treatment of the anginal syndrome.

The outstanding feature of the book is its series of anatomic drawings. These figures, prepared in collaboration with Dr. V. L. Lyons and drawn by Mrs. S. T. Johnson, show in progressive detail the complex network of sympathetic and vagal fibers which carry afferent impulses from the heart to the spinal cord. The drawings give an exceptionally clear, three-dimensional portrayal of the course of afferent fibers through the middle and inferior cardiac nerves to the corresponding cervical sympathetic ganglia, and their descent in the paravertebral sympathetic chains to the upper thoracic ganglia. Their central projection through the white rami communicantes and over the posterior spinal roots is equally well illustrated. This anatomic exposition is, however, open to one important criticism—the lack of emphasis on the role played by the thoracic cardiac nerves. The latter, which are so important in the neurosurgical treatment of angina pectoris, run directly across the posterior mediastinum to the upper ganglia of the thoracic sympathetic chain. These connections are included in some of the figures, but no functional significance is indicated in any. Their omission is particularly glaring in Figs. 11 and 12. Semidiagrammatic drawings such as these should be self-explanatory, but it requires a careful perusal of the text to extract the fact that the thoracic cardiac nerves play an important role in pain transmission. In order to emphasize their importance, it is not necessary to do more than point out that before their discovery, a decade ago, cervical sympathectomy was in disrepute because it failed to relieve cardiac pain in at least a third of the patients submitted to operation.

As regards the chapter on surgical treatment, the text suffers somewhat from the fact that it includes no illustrative case histories, and no single surgical procedure is definitely favored. On the other hand, the discussion of medical treatment is unnecessarily detailed in a book like this, concerned, as it is, largely with the nervous pathways; an important omission among the details is the failure to point out the great value of digitalis, at times lifesaving when acute congestive failure complicates coronary thrombosis; coramine is given far too much credit.

The bibliography is comprehensive and for the most part satisfactory, but there are only two brief references to the extensive work of Leriche and no mention of O'Shaughnessy's new method of cardio-omentopexy.

In estimating the value of the book as a whole, it can be recommended highly for the technical clarity of its portrayal of the cardiac nerves, but the description of medical and surgical therapy adds little to that of previous publications.

JAMES C. WHITE

CARDIOVASCULAR DISEASES. THEIR DIAGNOSIS AND TREATMENT. By David Scherf, M.D., and Linn J. Boyd, M.D., Associate Professor of Clinical Medicine, and Professor of Medicine, respectively, The New York Medical College, Flower and Fifth Avenue Hospitals, New York. St. Louis, 1939, 431 pages, The C. V. Mosby Co.

Except for slight changes in the order of the chapters, this book is essentially a translation of the fourth edition of Scherf's "Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen," published in 1938, and reviewed in this JOURNAL (16: 260, 1938). There have been a few minor additions, of which the least valuable are in the section dealing with congenital defects.

As a series of disconnected lectures to postgraduate students, the volume of Scherf was of some interest in presenting the current viewpoint of the Viennese school on certain aspects of cardiology. As a monograph on the diagnosis and treatment of cardiac and peripheral vascular diseases it is inadequate, and inferior to a number of texts already available in English. Incidentally, the translation, in places, is far from smooth. For example, on page 373, occurs this sentence: "The supervision of properly executed digitalis therapy belongs among the most important therapeutic acts of the physician."

No bibliography is given; only the briefest reference is made to electrocardiography and roentgenologic examination; there are ten text figures. Etiologic classification is ignored, both in arrangement of material and discussion. It is a record of personal experience on selected topics. The clinical descriptions are concise and clear. There are specific recommendations with regard to therapy.

The book is intended chiefly to serve as a handy guide for the "busy practitioner," but it does not fill a gap in the literature of the subject, so that there was really no need for the translation.

ROBERT L. LEVY.

AKTUELLE KREISLAUFFRAGEN. 14. ÄRZTLICHER FORTBILDUNGSLEHRGANG IN BAD-NAUHEIM. By fourteen contributors. 1939, 169 pages, 81 illustrations, Theodor Steinkopff, Dresden and Leipzig.

This book contains fourteen papers given as postgraduate lectures at Bad Nauheim, Sept. 23 to 25, 1938, and deals with many subjects pertaining to the heart and circulation. In the order in which the papers appear, we have: (1) "Recent Advances in Hemodynamics," by Ph. Broemser. Observations are recorded on the pulse rate, blood volume, blood pressure, and peripheral resistance during exercise, with trained and untrained subjects. In the trained subject, the pulse rate changed very little with effort, whereas the blood volume and minute volume increased. The systolic blood pressure was slightly elevated and the diastolic decreased. The effect of adrenalin was much more rapid in the trained than in the untrained subject.

(2) "The Control of the Circulation," by Eb. Koch. This is a verbose and highly academic discussion of some well-known, as well as unknown, factors controlling the circulation to various parts of the body.

(3) "Clinical Problems of Pulmonary Circulation," by Max Hochrein, a discussion—not at all profound, and quite rambling—of the physiology of the pulmonary circulation, with an attempt to explain such clinical entities as pulmonary edema, pulmonary embolism, etc.

(4) "The Question of Heredity in Cardiovascular Pathology," by Wm. Weitz. The author considers that heredity plays a role in the etiology of the following: Congenital heart and vascular defects, such acquired heart lesions as rheumatic heart disease and coronary disease, cardiac neurosis, essential hypertension and hypotension, thromboangiitis obliterans, varices, and hemophilia.

(5) "Dilatation and Hypertrophy of the Heart," by Eugene Kirch. A sound discussion of the subject, both from the clinical and experimental standpoint. The term "myogenic dilatation" is used to denote cardiac dilatation resulting from degenerative changes in the myocardium, and "tonogenic dilatation," an increase in the heart cavity in the absence of myocardial disease.

(6) "The Treatment of the Irregular Heart," by Ernst Edens. Most attention is paid to the treatment of auricular fibrillation, but nothing new is advanced. The author is much impressed by the effects of strophanthin intravenously in cases of auricular fibrillation with rapid ventricular rate and congestive failure. He advises strophanthin instead of digitalis in chronic fibrillation with slow ventricular rate and congestive failure. Paroxysmal auricular fibrillation is treated with strophanthin during and after the attack. Similarly, in cases of auricular flutter, the author states that strophanthin is more useful than digitalis or quinidine, a statement which many American clinicians will question. Ventricular extrasystoles occurring in damaged hearts are treated with strophanthin.

(7) "The Rôle of the Circulation in Surgery," by E. Rehn. A mediocre discussion dealing chiefly with postoperative shock and containing nothing new.

(8) "Operative Indications in Circulatory Diseases," by H. Bohnenkamp. The indications for operations in adhesive pericarditis are presented. A dscussion is given of the treatment of angina pectoris by sympathectomy and total thyroidectomy, two procedures now largely abandoned in America. Some attention is paid to nerve section and injection of veins in the management of peripheral vascular disease, but nothing new is advanced.

(9) "Circulatory Questions in Pediatrics," by W. Keller. The author speaks of childhood vasoneurosis, under which he includes the changes in the circulation that occur when the body is brought from the horizontal to the upright position.

(10) "Effect of Emotional Influences on the Course of Circulatory Disorders," by V. Weizsäker. A very general discussion of the influence of emotional and psychic factors on the clinical manifestations of cardiovascular disease.

(11) "The Influence of Respiration on the Intrathoracic Veins and Lymphatics," by W. Pfuhl. The author takes several pages to explain the well-known aspirating effect of the negative pressure in the thorax on the return circulation to the heart.

(12) "New Roentgen Results," by W. Böhme. The author relates his observations on the blood flow through the heart made with the roentgenkinematograph, and emphasizes the value of the method in the study of circulatory problems.

(13) "The Importance of Recording the Heart Sounds," by A. Weber. A method for the optical registration of the heart sounds is presented, but the author overestimates the diagnostic value of heart sound records.

(14) "The Dietetic Treatment of Cardiac Patients," by H. Eppinger. In spite of the title, the author pays little attention to the diet, but confines his remarks to the treatment of cardiac edema with drugs. For congestive failure, he advises a diet rich in potassium and poor in sodium chloride.

Apparently compiled for the practitioner, as suggested by the title, this book, with the exception of the paper by Edens on "The Treatment of Cardiac Irregularities," contains little material of practical importance to the practitioner of medicine. The theoretical discussions of the various subjects are at times verbose and contain nothing new.

R. W. Scott.

Symposium on the Synapse: By Herbert S. Gasser, Joseph Erlanger, Detlev W. Bronk, Rafael Lorente de Nó, and Alexander Forbes. 111 pages, 57 illustrations, $2.00, Charles C. Thomas, Springfield and Baltimore, 1939.

This is a symposium on the mechanisms of nervous transmission across synapses by the American scientists best qualified to discuss the subject. The papers were

first given before the American Physiological Society, at Toronto, in April, 1939, and later published in the *Journal of Neurophysiology*. This volume is a reprint.

The material given is the "last word" on its subject. It concerns students of the heart and circulation only because these organs contain, and are influenced by, nervous mechanisms presumably of the character here described.

ISAAC STARR.

THE PATIENT AS A PERSON: By G. Canby Robinson, M.D., LL.D., Sc.D., Lecturer in Medicine, Johns Hopkins University. The Commonwealth Fund, 1939, 440 pages, $3.00. London, Humphrey Milford, Oxford University Press.

The discovery, which Dr. Robinson makes in this book, that the hospital patient has a life apart from that in the ward, discloses a certain amount of naïveté. It is similar to the recent discovery which the psychoanalysts have made, namely, that their patients possess a body as well as a conscious and unconscious mind, psychosomatic medicine. However, both discoveries possess this in common—that while the social components of disease, on the one hand, and the physiologic components of emotion, on the other, have been recognized since the time of Hippocrates, and before, nothing much has been done about it. These problems have been stated but not answered. Dr. Robinson proposes to do something about it.

In this very readable book, he gives the results of a careful social study of 174 patients from the dispensary and wards of the Johns Hopkins Hospital. The title is intriguing, the material interesting and well presented. While the subject is not new, especially to the physician in general practice, who daily appraises the personality and social problems of his patients in their own home and family setting, the emphasis on it is stimulating and refreshing. It should have a particular appeal to younger medical students and their full-time academic instructors. The methods used in this study are admirable, paralleling the careful collection and analysis of data in any thoughtfully planned clinical investigation. It is an important contribution to the understanding and control of social adversity.

The 174 patients are classified in various disease categories: those with circulatory, respiratory, and digestive symptoms, respectively; the diabetic, the nephritic, the epileptic, etc. "The book is based upon information obtained directly from individual patients from their own accounts of the circumstances of their lives and from observing them in the hospital and in their homes." Dr. Robinson "made nearly all of the initial interviews and home visits himself." He found "personal inadequacy" as the one basic adverse condition in most of his patients. "Negro patients showed much less severe reactions to adversity as evidenced by worry, anxiety, and emotional strain."

In the patient with circulatory symptoms, Dr. Robinson believes that the "basic problem presented . . . is the adjustment of his life to his physical limitations, so that he may live constantly within these limitations and at the same time achieve a maximum of usefulness, efficiency, and happiness as a member of his social group." In the case of these patients with cardiovascular disease, he concludes: "It is clear that consideration of social and emotional disturbances, while by no means replacing rest, physical hygiene, and the judicious use of digitalis and other drugs, should constantly take an equal place beside them."

The patients with respiratory symptoms disclose other interesting, somewhat specific reactions: "The effect on respiration of the major emotions of fear, anger, disgust, wonder, and pleasure is a matter of common knowledge, but less

is known about the relation of more prolonged forms of emotional strain to abnormal respiratory action, such as coughing, rapid and shallow breathing, and sighing.''

Of patients with digestive symptoms, he writes: ''It may be said, however, that they show quite clearly the relationship of emotional disturbances to digestive symptoms both when organic disease is present and when no evidence of it is found.''

In the final chapter on the treatment of the patient as a whole, Dr. Robinson concludes that in the teaching hospitals throughout this country a department covering the social aspects of illness should be established, similar to that recently developed in the University of Brussels, under the direction of Professor René Sand.

This book can be heartily recommended to those interested in the social background and emotional factors of disease. The material collected and presented by a physician has a slightly different flavor than that of similar studies made by trained social workers (''The Social Component in Medical Care,'' by Janet Thornton and Marjorie Knauth). In considering the patient as a person, in addition to the emphasis on social adversity, one might wish for more data on his ''personal inadequacy''—his emotional life, his conscious and unconscious drives, his childhood and adult patterns of conduct, his conflicts and frustrations, his total personality.

WALTER W. HAMBURGER.

Announcements

REVISED CARDIAC CLINIC DIRECTORY NOW READY FOR DISTRIBUTION

It is announced by the New York Tuberculosis and Health Association that a revised, up-to-the-minute directory of the city's affiliated cardiac clinics is just off the press and ready for general distribution. The directory, compiled by the Heart Committee of the Association, covers the entire city, lists all cardiac clinics affiliated with the New York Heart Association, notes the clinic chiefs and social workers connected with each hospital, and quotes the hours the various clinics are at the public's disposal. For the first time, it carries a list of employment services and rehabilitation bureaus available to those suffering from heart disease.

The directory is for the use of social workers, public health nurses, and teachers, and copies may be obtained free of charge at the offices of the New York Tuberculosis and Health Association, 386 Fourth Avenue, New York City.

REVISED EDITION OF STANDARD WORK ON HEART DISEASES JUST OFF PRESS

Far more comprehensive and containing twice as many pages as any of its predecessors, the revised Fourth Edition of the diagnostic criteria of the New York Heart Association, ''Nomenclature and Criteria for Diagnosis of Diseases of the Heart,'' is just off the press. This book, known in previous editions as the ''Criteria for the Classification and Diagnosis of Heart Disease,'' has long been regarded as the standard work of its kind both in this country and abroad, and its fundamental purpose is to develop a precise and scientific nomenclature for the diagnosis of heart disease. The first edition appeared in 1928.

This new edition dwarfs all its forerunners, including, as it does, an authoritative outline of the three closely related fields of electrocardiography, radiology, and pathology, in addition to all-important clinical material.

Of the new material that has not appeared in any earlier edition, probably the most important is the section titled "An Outline for the Pathological Diagnosis of Cardiovascular Diseases and Anomalies," comprising nine chapters, 100 pages, and 52 illustrations. It was developed by men who are recognized authorities in their field and represents several years of intensive work.

Another valuable new section—"Therapeutic Classification"—purposes to guide physicians, nurses, and others in regulating the physical activity of cardiac patients.

The text relating to the clinical classification and diagnosis of heart disease has been revised, and although all necessary descriptive titles, together with definitions and instructions for their proper use, have been retained, a great deal of new material has been added. Another innovation finds the functional disorders of the heart placed among the titles for the diagnosis of heart disease, agreeing with the Standard Classified Nomenclature of Disease.

Dr. Harold E. B. Pardee served as chairman of the committee which directed revision of the book, and his colleagues included Doctors Arthur C. DeGraff, Clarence E. de la Chapelle, Cary Eggleston, Charles E. Kossmann, Robert L. Levy, and John B. Schwedel.

Dr. de la Chapelle was chairman of the committee which contributed the section "An Outline for the Pathological Diagnosis of Cardiovascular Diseases and Anomalies." His associates were Doctors William C. Von Glahn, Irving Graef, Robert A. Moore, Douglas Symmers, B. Morgan Vance, and the late Louis Gross.

As has been the case in previous years, the New York Tuberculosis and Health Association has arranged to distribute the book through the American Heart Association, which has adopted the volume as its official text. Copies may be obtained from the American Heart Association, 50 West 50th Street, New York City, at $2.00 per copy. A limited number of Spanish translations are also available.

Corrigendum

In the article, "Convallan in Cardiac Therapy," by Ralph H. Major, M.D., and Lee H. Leger, M.D., which appeared in the October number of the Journal, Figures 3 and 4 (p. 446) should be transposed in order to correspond with the legends.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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